STRATEGIC COMBINATION OF TRANSITION METAL-CATALYZED REACTIONS FOR ECONOMICAL ONE-POT SYNTHESES OF *N*-HETEROCYCLES

By

Sandeep Narayan Raikar

M.S., Sri Satya Sai Institute of Higher Learning, 2005

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Helena C. Malinakova, *chairperson*

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Jon A. Tunge

_____

Richard S. Givens

_____

Minae Mure

_____

Thomas E. Prisinzano

Date Defended: July 12, 2013

The Dissertation Committee for Sandeep Narayan Raikar
certifies that this is the approved version of the following dissertation:

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Committee:

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_____
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_____
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_____
Minae Mure

_____
Thomas E. Prisinzano

Date Approved:

Abstract

Sandeep Narayan Raikar, Ph.D.

Department of Chemistry, July 2013

University of Kansas

There has been extraordinary progress in the field of chemical synthesis over the last couple of decades. Innovative methodologies and robust catalysts are emerging. Propelled by all these inventions the evolution of the field has reached the state when the principle concern of a synthetic chemist is not whether a molecule can be synthesized, but how rapidly and economically can it be produced. In this regard the development and application of one-pot reactions and multicomponent reactions play a major role because of their excellent overall economy of operation. The goal of this dissertation is to expand our understanding of regiocontrol of known transition metal-catalyzed reactions, and design one-pot protocols towards syntheses of medicinally relevant heterocycles.

The first project described in chapter 2 of this dissertation, demonstrates the development of a synthetic method utilizing a Pd-catalyzed multicomponent reaction (MCR) previously developed in our laboratory for synthesis of highly substituted pyrrolidines and tetrahydrofurans. The project also helped us to unequivocally assign the relative stereochemistry of the precursors proposed in our previous reports. Methodology reported herein opens up possible future application towards synthesis

of potent ET_A antagonist-atrasentan and natural products like kainic acid and acromelic acid.

The second project described in chapter 3, illustrates the concept of strategic sequencing of a MCR with transition metal-catalyzed annulation reactions. Herein, Cu-catalyzed MCR of imine, acid chloride and terminal alkyne was used to assemble highly functionalized enynes which upon ring closing enyne metathesis and Heck cyclization delivered *N*-heterocycles such as benzoindolines, dihydro pyrroloquinolines, cyclopropane fused dihydro indenopyridines and phenanthrolines. Divergence in an unexpected 5-*exo* vs 6-*endo* pathway during the Heck cyclization of homologous or isosteric substrates was observed. We believe the substrate conformation and the chelation are the factors which govern the regiodivergent Heck cyclization. A plausible mechanism for this regiodivergent Heck annulation is proposed.

The third project described in chapter 4, presents efforts towards the successful design of a sequential one-pot protocol for the enyne metathesis and Heck cyclization illustrated in project two. A sequential one-pot methodology was realized for Ru/Pd catalyzed annulation reactions. Optimization of a common solvent for dual metal catalysis and a suitable base for Pd catalysis proved to be critical. The yields of pure heterocycles obtained via one-pot protocol were 2-22% higher in comparision with the stepwise procedure.

.....to my Parents, my wife

....and all those who strive to make the society a better place to live

Acknowledgements

It would not have been possible to write this doctoral thesis without the help and support of the kind people around me.

Above all, I express my sincere gratitude to my advisor Prof. Helena Malinakova for her constant guidance and support for last five and half years. Along with teaching chemistry you guided me in how to prepare and deliver a talk which I believe was a worthwhile learning experience. Thank you for converting some of my mistakes into opportunities to teach few important lessons of life.

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My sincere gratitude to all the other professors in the department of chemisty and the administrative staffs especially -Sonjia Payne and Beverly Johnson. Lastly I thank the department of chemistry and the University of Kansas for giving me a wonferful opportunity to study science.

Strategic Combination of Transition Metal-Catalyzed Reactions for the Economical One-Pot Syntheses of *N*-Heterocycles

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Abbreviations

Å	angstrom
μwave	microwave radiation
μL	microliter(s)
3CC	three-component coupling
9-BBN	9-borabicyclo(3.3.1)nonane
Ac	acetyl
ACN	acetonitrile
AIBN	azobisisobutyronitrile
Ar	aryl
Atm	atmosphere(s)
(*S*)-BINAP	(*S*)-2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Bu	butyl
BQ	benzoquinone
t-Bu	*tert*-butyl
Bz	benzoyl
cat.	Catalyst
Cbz	carboxybenzyl
CM	cross metathesis
Cy	cyclohexyl
d	day(s)

dba	dibenzylideneacetone
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	dimethyl sulfoxide (deuterated)
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
E	electron withdrawing group
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent(s)
Et	ethyl
et al.	and others
FAB	fast atom bombardment
g	gram(s)
GC-MS	gas chromatography - mass spectrometry
h	hour(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence

HMBC	heteronuclear multiple bond correlation
IR	infrared spectrometry
KHMDS	potassium bis(trimethylsilyl)amide
LG	leaving group
L	ligand
Me	methyl
M	moles per liter
MHz	megahertz
min	minutes
mg	milligram(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	4 Å molecular sieve
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NR	no reaction
Nu	nucleophile
Pdt	product

PG	protecting group
Ph	phenyl
PMP	*p*-methoxy phenyl
ppm	parts per million
i-Pr	*iso*-propyl
R_f	retention factor
RCM	ring-closing metathesis
RCEYM	ring closing enyne metathesis
SM	starting material
STMC	sequential transition metal catalysis
rt	room temperature
TBAB	tetra-*n*-butylammonium bromide
TBAC	tetra-*n*-butylammonium chloride
TBDMS	*tert*-butyldimethylsilyl
TBME	*tert*-butyl methyl ether
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

Chapter One

Prologue

The rapid generation of molecular complexity and diversity from simple and readily accessible starting materials is a contemporary research theme in the practice of modern organic synthesis. Along with achieving efficiency in syntheses, it's high time that organic chemists considered its effects on the environment and the economy of synthesis.

In this context, our group utilizes the concept of combining multicomponent reaction with efficient post-transformation sequences typically performed as one-pot processes for the synthesis of complex heterocyclic compounds. A multicomponent reaction offers not only great molecular complexity and diversity per step but also the possibility of introducing matched functionalities suitable for further transformations. With one-pot reactions comes increased operational simplicity as well as reduction in energy and materials usage and waste output, with the purification of intermediates at each step no longer needed. However, the one-pot protocols have proven to be particularly difficult when transition metal-catalyzed reactions were involved due to the likelihood of catalyst poisoning in complex reaction mixtures.

The following paragraphs describe the layout and content of this dissertation. Part I of chapter two outlines the importance and types of one-pot protocols with recent examples involving either sequential Ru or Pd-catalyzed reactions followed by fundamental concepts to be considered while designing one-pot processes. Part II of chapter two portrays various methodologies incorporating multicomponent and transition metal-catalyzed reactions towards synthesis of highly substituted pyrrolidines, tetrahydrofurans and benzofused *N*-heterocycles. Part III of chapter two

overviews mechanistic aspects of ring closing enyne metathesis reaction and part IV illustrates the factors controlling regiochemistry in an intramolecular Heck cyclization.

The remaining chapters describe the challenges, solutions, results and experimental work accomplished in this dissertation. Chapter three describes our efforts aimed at demonstrating the synthetic utility of the Pd-catalyzed multicomponent reaction (MCR) previously developed in our laboratory for the synthesis of highly substituted pyrrolidines and tetrahydrofurans which are prevalent in variety of medicinally significant natural products and synthetic pharmaceutical agents.

Chapter four discusses our construction of benzofused *N*-heterocycles via sequencing Cu-catalyzed MCR with sequential Ru and Pd catalysis and uncovering of an unexpected 5-*exo* vs 6-*endo* regiodivergent Heck cyclization.

Chapter five presents our efforts towards the successful designing of sequential one-pot protocol for the Ru/Pd catalysis discussed in chapter four.

Chapter two

Introduction

Part I

One-Pot Reactions and Sequential Transition Metal Catalysis

2.1 **One-pot Reactions: Economy in Synthesis**

An important concern in any chemical process is the yield of a particular transformation – the effectiveness of converting given substrate into a single desired product. Modern organic synthesis faces other challenge of designing practical and efficient approaches to the most complex naturally occurring or synthetic medicinally relevant compounds. The conventional approach in organic synthesis is the stepwise formation of individual bonds to attain the desired target. Such a process requires the purification and isolation of intermediates at each step. As the number of steps increases there is potential loss in yield and efficiency. Thus, increasing the efficiency and minimizing the wastes is the need of the hour.[1]

An attractive solution towards this problem would be strategically sequencing the powerful carbon-carbon bond-forming reactions that would proceed in one-pot without multiple isolation and purification steps.[2-3] With one-pot reactions comes increased operational simplicity as well as reduction in energy and materials usage and waste output, with the purification of intermediates at each step no longer needed. Also, intermediates need not be stable enough for isolation; because they are quickly transformed by a subsequent reaction into a lower energy species.[4] The use of one-pot reactions has obvious benefits both environmentally and economically.

In particular, sequential transition metal-catalyzed reactions are well-suited for one-pot processes due to their broad range of carbon-carbon bond formation and functional group tolerance.[5-6] Sequential transition metal-catalyzed reactions have been successfully employed in the synthesis of diverse heterocycles[7-9] as well as

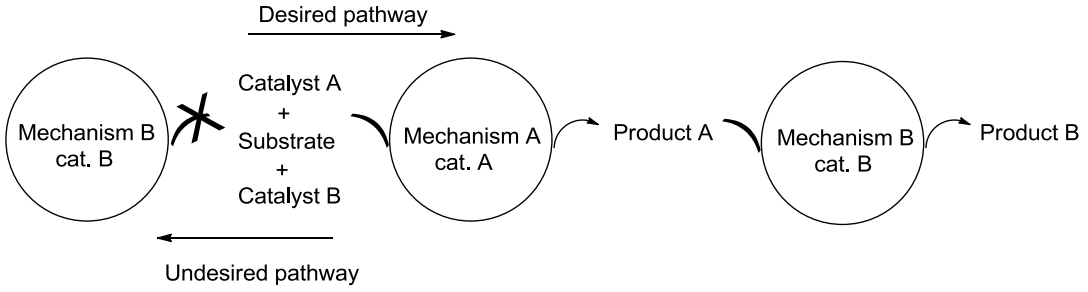
complex natural products.[10-11] Moreover, along with sequencing with other metal catalyzed reactions, transition metal catalysis can be sequenced with bronsted acid catalysis,[12-15] organocatalysis,[16-18] and enzyme-catalyzed[19-21] reactions.

One-pot reactions can be broadly classified as:

1) Combined or Concurrent one-pot reactions.

Combined one-pot reactions are the processes involving sequential transformation of a substrate via two or more mechanistically distinct pathways by two or more functionally distinct, and ideally non-interfering, catalysts (Figure 2.1).[17] Another important criterion is that all the reaction components and catalysts are present at the outset of the reaction. There is no further addition of reagents or modification of conditions on commencement of the reaction. Thus monitoring of formation and isolation of the intermediate is not necessary. An important challenge in combined one-pot reaction is to avoid the unproductive path, wherein the second catalyst in the sequence reacts with the substrate.

Figure 2.1

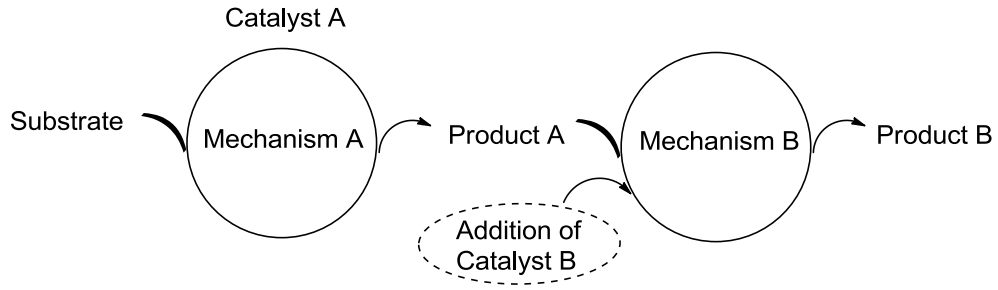


2) Sequential one-pot reactions.

Sequential one-pot reactions differ from combined one-pot reactions wherein another reagent, mediator, catalyst is added or the reaction condition is modified after the

initial transformation without purification of the product from the prior step. The subsequent reaction steps then lead to the final product (Figure 2.2). These are less challenging when compared to combined one-pot reactions. Although some operational simplicity is lost; the benefits associated with combined one-pot reaction remain.

Figure 2.2



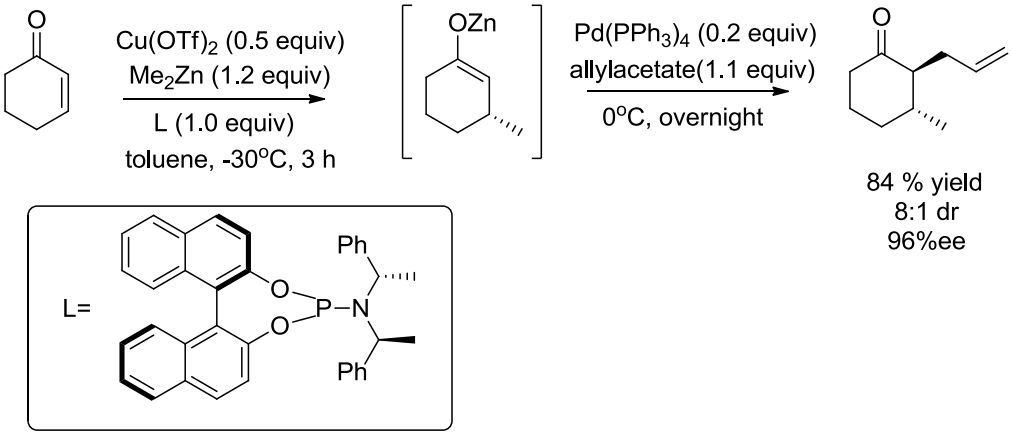
2.2 **Overview of Recent Applications of One-Pot Reactions Involving Pd or Ru**:

Initially, research into transition metal catalysis concentrated on the development of a single, highly selective and high yielding step. There are lots of carbon-carbon, carbon-hydrogen and carbon-heteroatom bond forming reactions known today. Subsequently metal catalysts have been applied to sequential reactions. As stated earlier they can be also sequenced with bronsted acid catalysis,[12-15] organocatalysis,[16-18] and enzyme-catalyzed[19-21] reactions. Unsurprisingly, palladium catalysts have been employed in the majority of metal-catalyzed sequential reactions. Since my research involves Ru and Pd-catalyzed sequential reactions, this overview mainly pertains to Ru and Pd catalysis.

2.2.1 **Sequential Cu/Pd Catalysis**:

Feringa *et al*. reported a short, catalytic asymmetric synthesis of (-)-pumiliotoxin C. The key step of the sequence was a Cu/Pd catalyzed tandem asymmetric conjugate addition–allylic substitution reaction (Scheme 2.1).[22]

Scheme 2.1

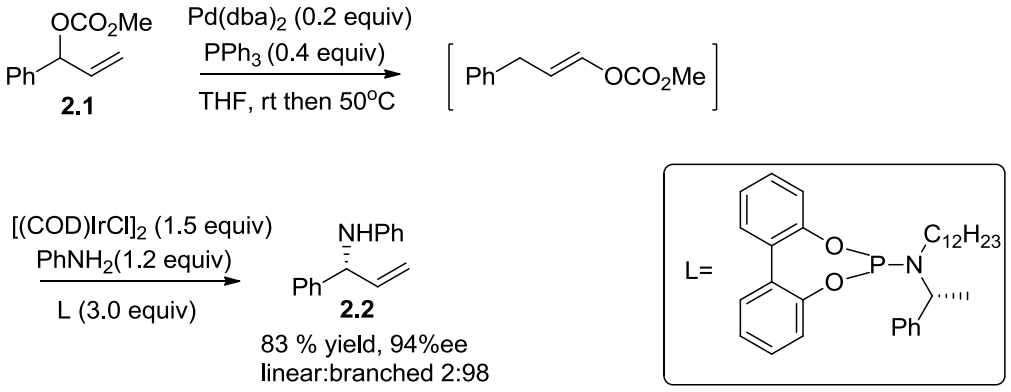


The palladium catalyst and allylacetate were added after the completion of the catalytic asymmetric Michael addition of Me_2Zn to cyclohexenone, to prevent the possible catalyst interference. The reaction created two stereocenters with excellent enantioselectivity and high diastereoselectivity.

2.2.2 **Sequential Pd/Ir Catalysis**:

Hartwig *et al*. developed a sequential palladium-catalyzed isomerization and iridium-catalyzed asymmetric allylic substitution reaction (Scheme 2.2).[23]

Scheme 2.2

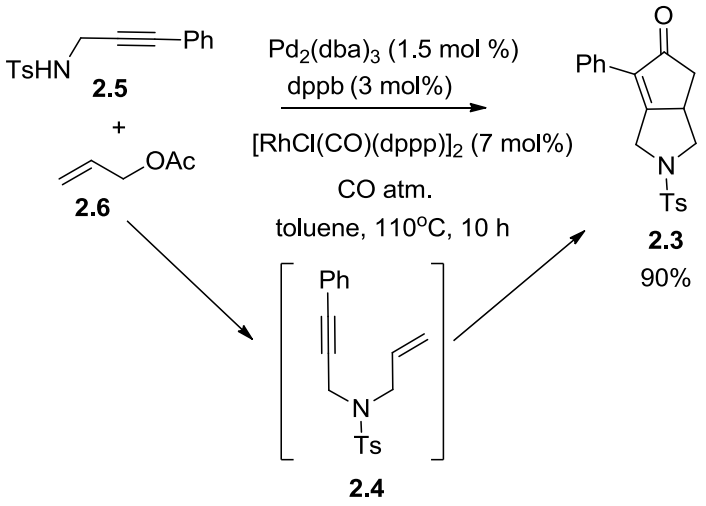


This tandem reaction allows the conversion of easily synthesized branched aromatic carbonates **2.1** to branched allylic aromatic amines **2.2** in good yield and excellent regio and enantioselectivity. Simple filtration of the crude product through silica was needed to remove the bulk of palladium catalyst before the addition of chiral ligand, iridium catalyst, and nucleophile. This was to prevent the interference of palladium with chiral iridium catalyst to secure high yield and enantiomeric excess of the final product.

2.2.3 **Sequential Pd/Rh Catalysis**:

Jeong *et al.* reported[24] sequential palladium and rhodium catalysis to synthesize functionalized bicyclopentenone **2.3**. This transformation includes two reactions; the first allylation generates an enyne intermediate **2.4** via the Pd π-allyl complex from the mixture of propargyl amine **2.5** and allyl acetate **2.6**. Subsequent Pauson-Khand type reaction of the resultant enyne yields bicyclopentenone (Scheme 2.3).

Scheme 2.3

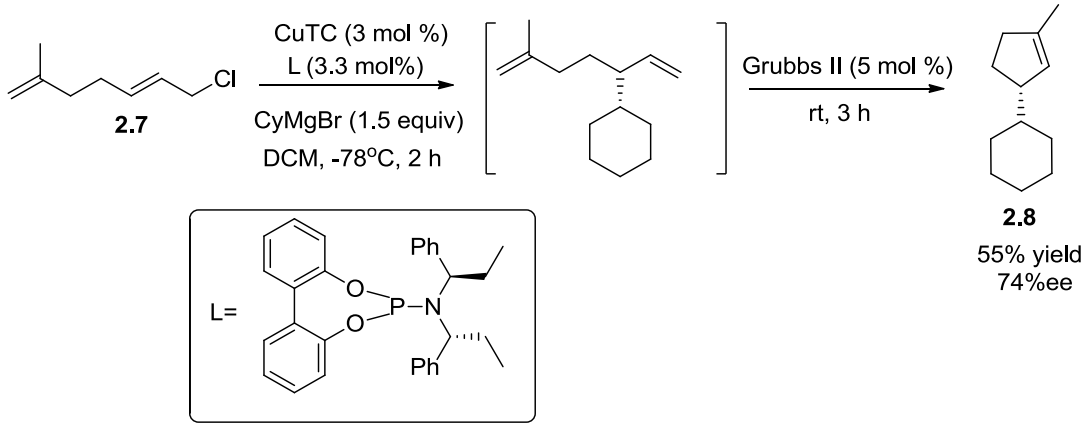


With careful optimization of ligand, solvent and temperature the sequence was performed as a combined one-pot operation. It was found that catalysts $[RhCl(CO)_2]_2$ and [RhCl(CO)dppe] were not compatible with $Pd(dba)_2$/dppb and suppressed the first allylation reaction. $[RhCl(CO)(dppp)]_2$ and $[RhCl(CO)(dppb)]_2$ (generated in situ by mixing of $[RhCl(COD)]_2$ and dppb) were compatible with the presumed Pd(dppb). The author claims an improvement in the yield of 10% when compared to the stepwise process.

2.2.4 **Sequential Cu/Ru Catalysis**:

Alexakis *et al*. developed a new strategy using ω-ethylenic allylic substrates **2.7** to access highly enantioenriched cyclopentenes **2.8** via a one-pot enantioselective allylic alkylation and ring-closing metathesis (Scheme 2.4).[25] The work demonstrates the use of an ω-ethylenic allylic substrate as synthetic equivalent, which can undergo copper-catalyzed asymmetric allylic alkylation using Grignard reagents and bears a convenient functionality to be cyclized through a ring closing metathesis reaction.

Scheme 2.4



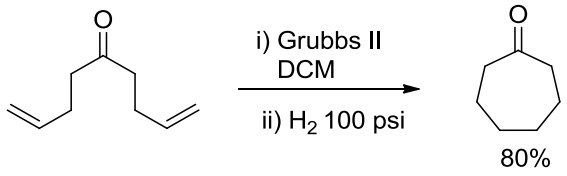
The asymmetric allylic alkylation was performed in dichloromethane at -78°C and after completion of the reaction monitored by gas chromatography, without quenching the Grubbs catalyst was added and the flask was warmed to room temperature. The author notes that the metathesis step was the most delicate and needed recently bought (or prepared) Grubbs catalyst.

2.2.5 **Grubbs Catalyst in Sequential Reactions**:

The ruthenium metathesis catalysts developed by Grubbs and co-workers[26] have proven to be very effective in sequential reactions. McLain and co-workers found that an ethylene/methacrylate copolymer formed by ring-opening metathesis polymerisation using Grubbs-I catalyst could be successfully hydrogenated simply by placing the reaction vessel under an atmosphere of hydrogen (400 psi) after the polymerisation took place.[27] Studies by Fogg have shown that the treatment of the catalyst with hydrogen forms the known hydrogenation catalyst $RuCl_2(H_2)(PCy_3)_2$.[28] The Grubbs research group incorporated the findings of McLain and Fogg, and used this methodology in a small molecule synthesis.[29] They showed that both the first or

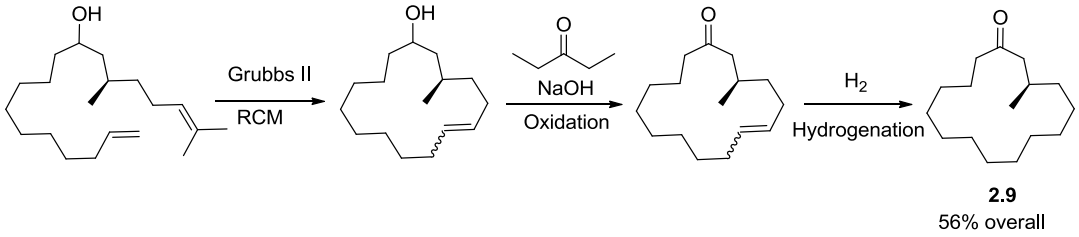
second generation metathesis catalysts were able to mediate either ring-closing or cross metathesis followed by hydrogenation (Scheme 2.5).

Scheme 2.5



Extending the concept, Grubbs also found that these complexes act as a precatalyst for both the oxidation of alcohols and the reduction of ketones via transfer hydrogenation. Addition of base and a suitable hydrogen donor such as 2-propanol, led to reduction of ketones, or a suitable acceptor such as 3-pentanone led the oxidation of alcohols. Grubbs demonstrated the utility of this trifunctional catalyst in the synthesis of (*R*)-(–)-muscone **2.9** (Scheme 2.6), in which ring closing metathesis (RCM) followed by oxidation and hydrogenation was achieved with a single catalyst in one pot.[13]

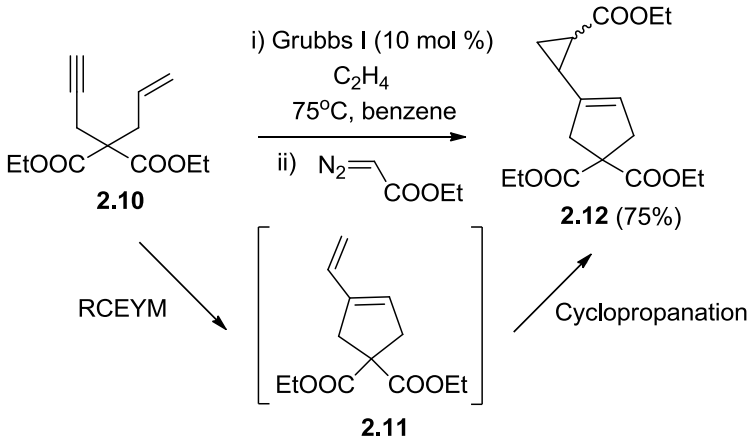
Scheme 2.6



Snapper and co-workers in 2006 reported tandem ring closing enyne metathesis (RCEYM) and cyclopropanation reaction to synthesize vinyl cyclopropanes (Scheme 2.7).[30] Treatment of enyne **2.10** with Grubbs-1 catalyst under an atmosphere of

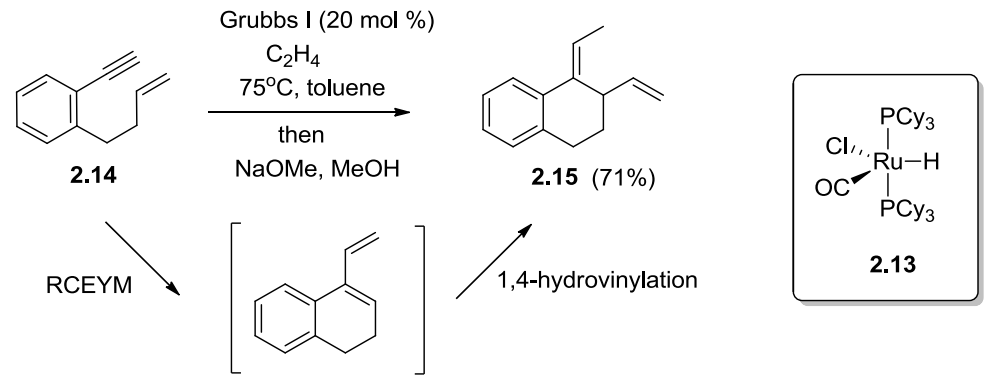
ethylene formed diene **2.11**, to which was added ethyl diazoacetate and caused cyclopropanation of the terminal alkene to afford the desired product **2.12** in 75% yield and a 1:1 ratio of E/Z isomers.

Scheme 2.7



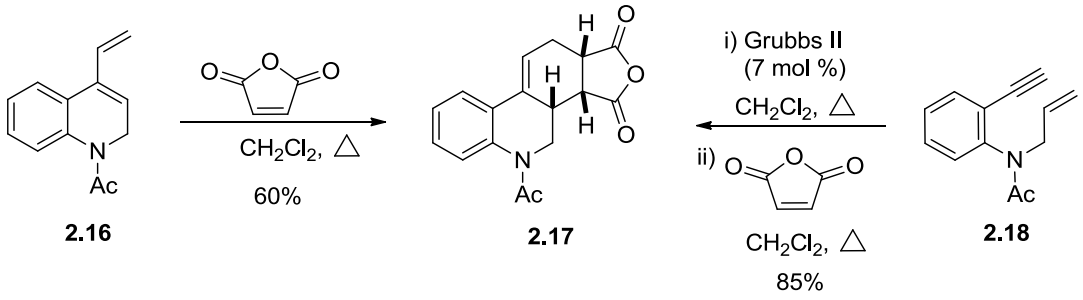
Yi and co-workers showed that ruthenium hydride complex **2.13** could facilitate the hydrovinylation of 1,3-dienes.[31] Furthermore, this ruthenium hydride complex can be formed by reaction of Grubbs-I catalyst with a primary alcohol and an inorganic base.[32] Thus, Snapper and co-workers proposed the development of a tandem RCEYM followed by hydrovinylation reaction catalyzed by Grubbs-I catalyst. Treatment of enyne **2.14** with Grubbs-I catalyst under an atmosphere of ethylene, followed by addition of sodium methoxide and methanol afforded the 1,4-hydrovinylation product **2.15** exclusively in good yield (Scheme 2.8).[33]

Scheme 2.8



Taking advantage of 1,3-diene motif created during RCEYM, Perez-Castells and co-workers explored the possibility of combining enyne metathesis with a Diels-Alder reaction.[34] The group showed that by carrying out an isolated Diels-Alder reaction on diene **2.16**, the tetracyclic product **2.17** was formed in 60% yield (Scheme 2.9). However, by carrying out a tandem RCEYM reaction catalyzed by Grubbs-II catalyst, followed by the same Diels-Alder reaction, the desired tetracyclic product was afforded in 85% yield from enyne **2.18** under the same reaction conditions. These results would suggest that the presence of the ruthenium is assisting the Diels-Alder reaction resulting in a more efficient process.

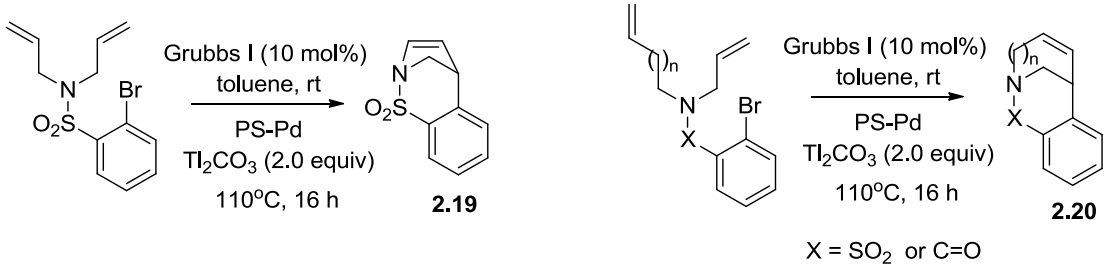
Scheme 2.9



2.2.6 **Examples of Ru Catalyzed Metathesis Reactions Followed by a Pd Catalyzed C-C Bond Forming Reactions**:

Grigg and co-workers in 2000, reported combined as well as sequential one-pot RCM/Heck reaction (Scheme 2.10).[35] The Ru and Pd catalysts could be added either sequentially, or in combination delivering comparable product yields (62% and 65%) during the preparation of bridged *N*-heterocycles **2.19** with a five-membered ring. However in preparations of *N*-heterocycles **2.20** with six- to eight-membered rings, the addition of the catalysts in combination caused a significant drop in the yields of the RCM/Heck sequence. To circumvent this problem polystyrene-bound (PS-bound) Pd catalyst was used which prevented the Ru poisoning by Pd catalyst species. More detail about this work is discussed in later (section 2.3 *vide infra*). However this solution is limited to sequences with facile RCM reactions that proceed at room temperature.

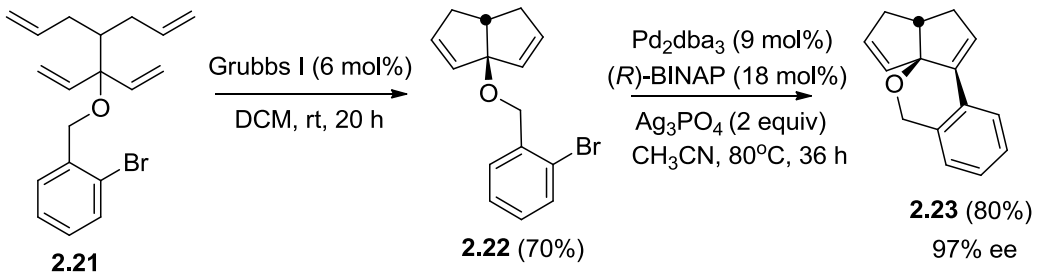
Scheme 2.10



one pot sequential catalysis	62% yield	48% yield (n=1), 69% yield (n=2)
one pot combination catalysis	65% yield	22% yield (n=1), 37% yield (n=2)
one pot combination catalysis with PS-bound Pd catalyst	71% yield	73% yield (n=1), 73% yield (n=2)

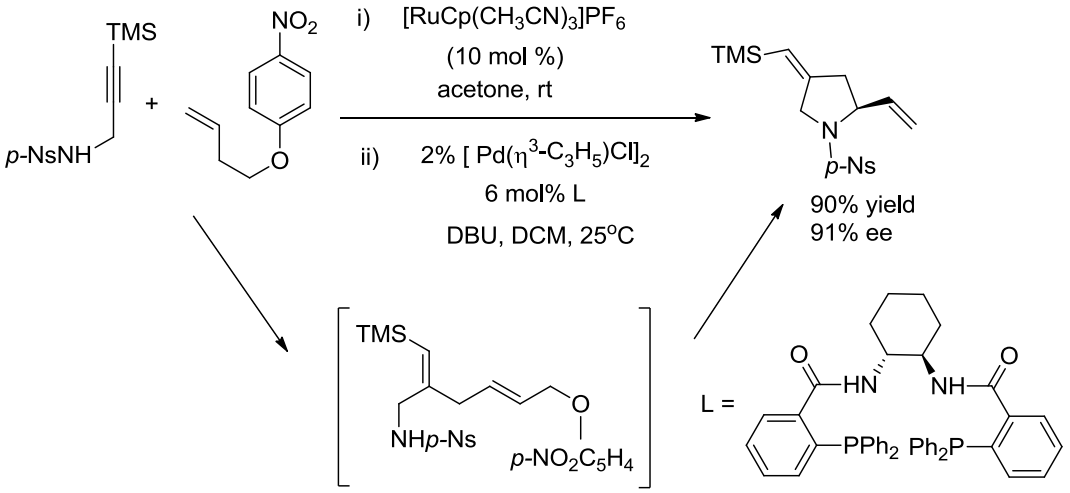
In 2004 Mark Lautens reported a sequential olefin metathesis and an intramolecular asymmetric Heck reactions.[36] A diastereoselective double ring closing metathesis of **2.21** using Grubbs-I catalyst afforded the bicylo-octadienes **2.22** in 70% yield. Upon subjecting to intramolecular asymmetric Heck reactions these bicyclodienes were converted to fused polycycles **2.23** with moderate to good yields and with good enantioselectivities (Scheme 2.11). However, Lauten had not reported any attempt of performing this sequence as a one-pot protocol.

Scheme 2.11



Trost *et al*. reported a sequential one-pot synthesis of enantio- and diastereopure *N*-and *O*-heterocyclic compounds using the combination of Ru catalyst and chiral palladium complex.[37] After the completion of ruthenium-catalyzed alkene/alkyne cross metathesis reaction, the chiral ligand and palladium catalyst were added to afford the enantioselective intramolecular heterocyclization reaction (Scheme 2.12). This tandem reaction was employed for the concise synthesis of ring B of bryostatin, a potent antitumor agent.

Scheme 2.12



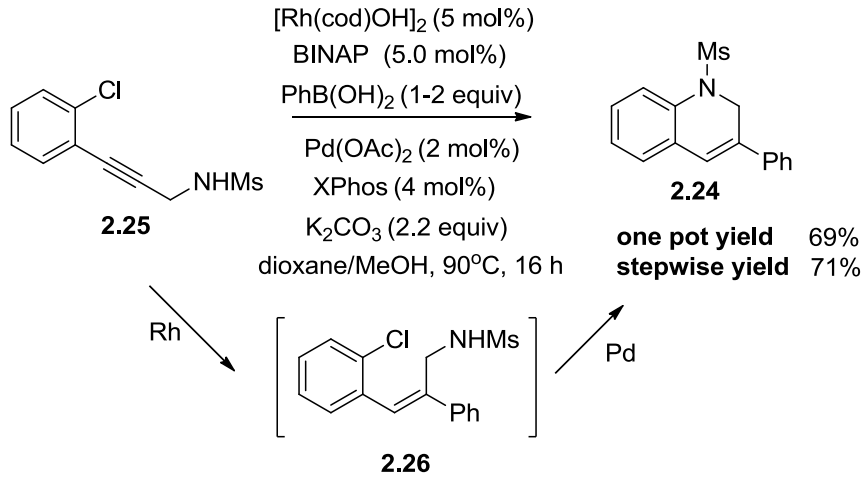
2.3 **Fundamental Concepts in Sequential Catalysis**:

Designing a one-pot catalysis sequence is challenging and more so in case of combined one-pot sequences. Several factors must be considered for coupling the activity of multiple catalysts in a sequential catalysis. The primary and most obvious being compatibility. There should be no interference or poisoning between the catalytic species in an ideal situation. Furthermore, the active site reactivity must be well matched so that the order of reaction sequence is followed properly. Similarly, if the activity of one catalyst is disproportionately low, then subsequent catalysts may become substrate starved; a condition that can result in decomposition or unwanted side reactions.

In this regard, Lautens described[38] an impressive systematic optimization of the auxiliary phosphine ligands for discrete Rh(I) and Pd(0) catalysts. The catalysts were added in combination that allowed for a sequential Rh-catalyzed alkyne arylation and Pd-catalyzed C-N coupling to be selectively performed as a "one-pot

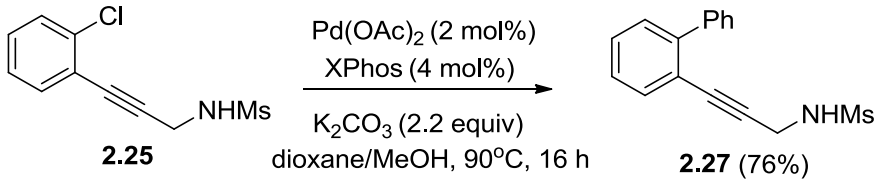
two-metal/two-ligand catalyst system" delivering substituted quinolines **2.24** (Scheme 2.13). The reason for success of this methodology was meticulous optimization of ligands, catalyst loading, Rh/Pd and the metal/ligand ratios.

Scheme 2.13



To survey the reactivity of the possible metal–ligand combinations, several control experiments were carried out on each step. Use of phosphine-free $[Rh(cod)OH]_2$ led primarily to the decomposition of the substrate **2.25**. Subjecting substrate to only [Pd(binap)] or [Pd(X-Phos)] did not lead to **2.26** or **2.24**; instead, [Pd(X-Phos)] furnished the Suzuki cross-coupling product **2.27** in good yield (76%) (Scheme 2.14). The arylation reaction using X-Phos as a ligand led to a low yield of **2.26** (5%) and a significant amount of decomposition (40%). The reaction of **2.26** with [Pd(binap)] yielded only trace amounts of **2.24**.

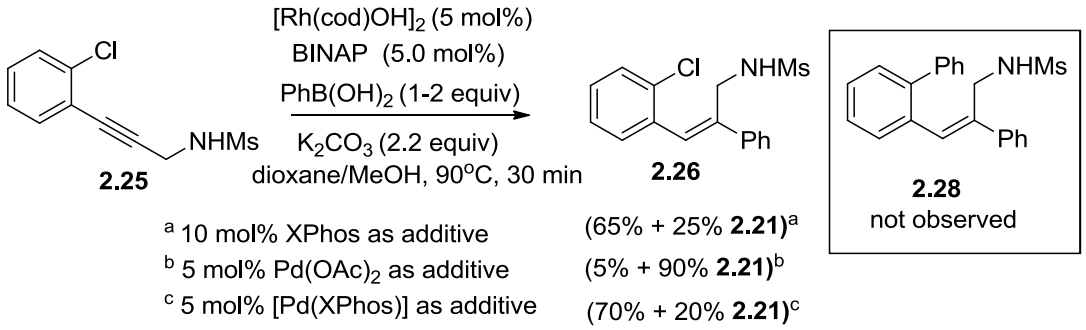
Scheme 2.14



From these control experiments it was apparent that use of [Rh(binap)] resulted in the desired intermediate **2.26**, and phosphine-free rhodium led to decomposition of **2.25**. The ability to form [Pd(X-Phos)] was equally important since [Pd(binap)] was catalytically inactive in C-N coupling. Thus the combination of Rh with BINAP and Pd with XPhos was established.

Next the effect of $Pd(OAc)_2$ or X-Phos addition on the rate of the alkyne arylation reaction was examined (Scheme 2.15). When the reaction was carried out with X-Phos present in the catalyst solution, a minimal effect on the rate of the reaction was observed affording 65% of **2.26**. In contrast, addition of 5 mol% of $Pd(OAc)_2$ led to the formation of only a trace of **2.26** (5%), while the conversion of **2.25** returned to more than 70% with the addition of 5 mol% of [Pd(X-Phos)] solution to the reaction mixture.

Scheme 2.15

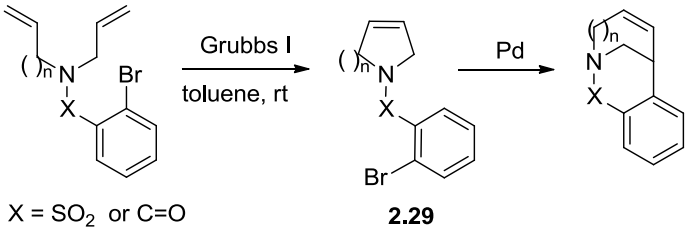


No Suzuki products containing the arylated alkene, such as **2.28**, were ever observed in the optimized reaction, thus indicating that even if an excess of the aryl boronic acid is used, the Suzuki coupling is slower than the intramolecular C-N coupling in **2.25**. This shows that it is important for [Pd(X-Phos)] complex to form at the initial stage of the one-pot reaction. So in the optimized conditions a premixed solution of $Pd(OAc)_2$ and XPhos was added to the reaction mixture. The premixing also avoided the problem of ligand exchange between [Rh(binap)] and [Pd(X-Phos)] thus ensuring a smooth C-N coupling in step two.

Under the optimized conditions (Scheme 2.13), the sequence proceeded in one vessel, in which both catalysts exist concurrently and display correct reactivity even though other reaction pathways, including a Suzuki reaction, are available. Interestingly the one-pot reaction proceeded in an overall yield of 69%, in comparison to the two-step combined yield of 71%.

Another important fundamental investigation that contributed towards designing a one-pot reaction was made by Grigg[35], discussed earlier (section 2.2.6 *vide supra*). The combined one-pot sequence successfully afforded compound **2.19** (Scheme 2.10 *vide supra*) in moderate yield using a RCM facile substrate. However, the yield significantly dropped in case of RCM challenging substrate compound **2.20** (Scheme 2.10, n=2). Control experiments indicated that the RCM catalyst was being inhibited by the addition of $Pd(OAc)_2$, Hermann's catalyst,[39] phoshine ligands, but unaffected by the carbonate bases (Table 2.1).

Table 2.1: Effect of additives on RCM



Entry	Additive	Amount	2.29 (%)[a]
1	None	NA	>95
2	$Pd(OAc)_2$	10 mol%	10
3	Herman's catalyst	10 mol%	<5
4	$Pd(PPh_3)_4$	10 mol%	<5
5	PPh_3	20 mol%	8
6	Cy_3P	20 mol%	5
7	K_2CO_3	2equiv	>95
8	Tl_2CO_3	2 equiv	93

[a] calculated from ^{1}H NMR

To address this problem, Grigg employed polystyrene-bound (PS-bound) Pd-catalyst, that could be used in combination with the Grubbs I catalyst to afford the entire range of bridged *N*-heterocycles in good yields. The author notes that the success of this method was due to poor polymer swelling at room temperature, limiting access of the Ru-catalyst to the palladium species and phosphine ligands. Thus the Ru-catalyst poisoning was prevented during the initial RCM reaction period. However, at higher temperature of Heck reaction (110^{o}C) the swelling increased allowing access to the Pd-catalyst and promoting efficient Heck cyclization. Thus, carrying out the RCM at room temperature and the Heck reaction (with polymer supported Pd, PS-Pd) at 110^{o}C, ensured that both catalysts could be added together and the desired cascade was achieved.

Part II

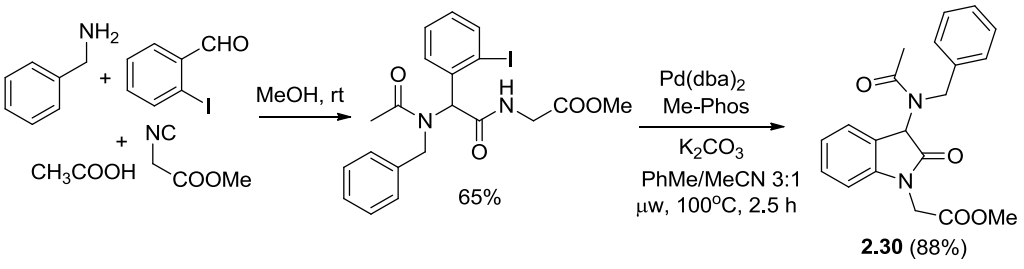
Sequencing Multicomponent Reactions and Transition metal catalysis: Methods for Synthesis of α-Arylated Pyrrolidine, Tetrahydrofurans and Benzofused Heterocycles

The area of drug discovery[40] and diversity oriented synthesis[41] have grown rapidly over the past decade. Hence, there is high demand for expedite and efficient generation of collections of organic compounds that are structurally and functionally diverse and possess skeletal frameworks found in natural products and drug-like molecules.[42] One of the promising ways to achieve this goal is by combining multicomponent reactions (MCRs),[43] with transition metal-catalyzed reactions. The MCRs allow for a rapid synthesis of differentially substituted intermediates from three or more reactants. Selective functional groups pairing of these intermediates via transition metal-catalyzed cyclizations can give access to diverse combinatorial libraries[44-45] of heterocycles.

2.4 **Sequencing MCR and Pd Catalysis**:

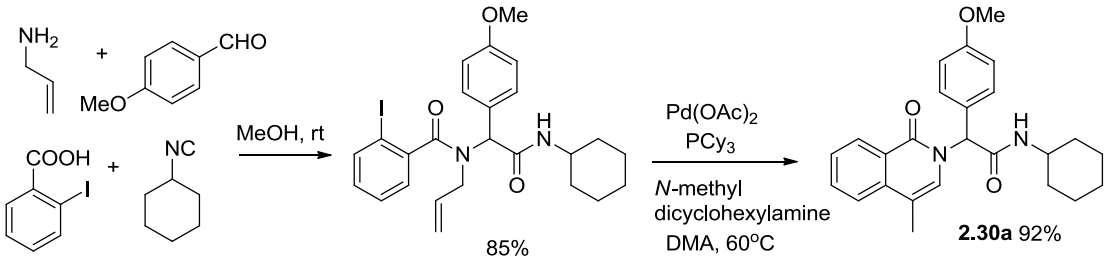
Many of the MCRs are name reactions, for example, Ugi, Passerini, Van Leusen, Strecker, Hantzsch, Biginelli.[43] Zhu in 2006 reported[46] a two-step sequence involving an Ugi four-component reaction and a palladium-catalyzed intramolecular amidation of aryl iodide for rapid access to functionalized oxindole **2.30** with four diversity points (Scheme 2.16). Microwave heating was used to accelerate and to improve the efficiency of the intramolecular Buchwald−Hartwig reaction

Scheme 2.16

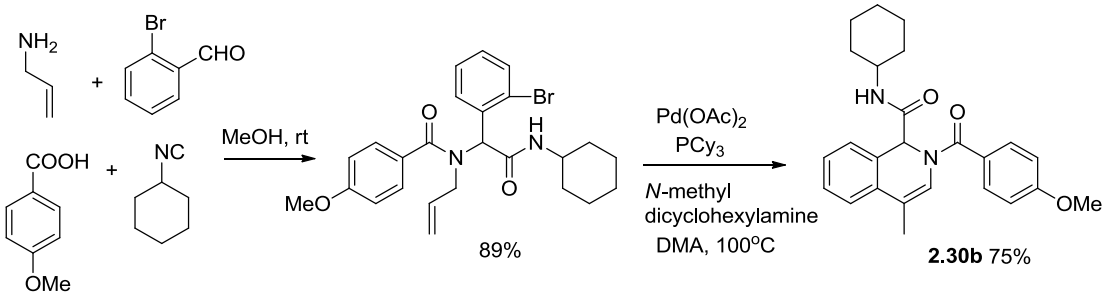


Yang *et al.* demonstrated the efficiency of sequencing MCR with a transition metal-catalyzed cyclization reaction. They reported synthesis of isoquinoline scaffolds **2.30a** and **2.30b** in a combinatorial format by sequencing the Ugi four-component reaction and the Pd-catalyzed intramolecular Heck reaction, from readily available starting materials (Scheme 2.17) and (Scheme 2.18).[47]

Scheme 2.17



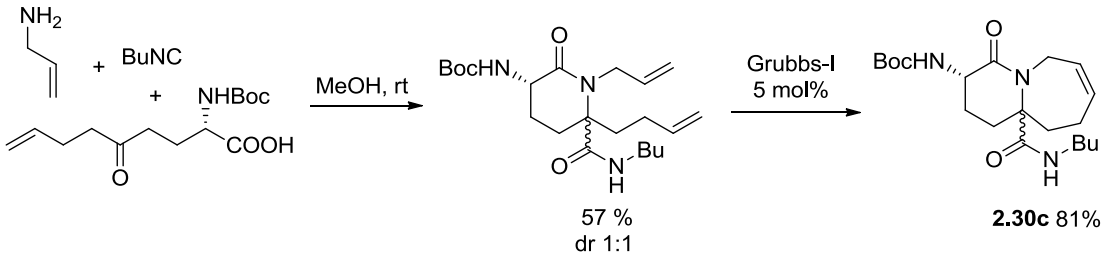
Scheme 2.18



2.5 **Sequencing MCR and RCM**:

Sequencing Ugi-MCR and ring closing olefin metathesis, Westermann reported[48] synthesis of bicyclic lactams **2.30c** , materials that can be used as peptide mimics (Scheme 2.19)

Scheme 2.19

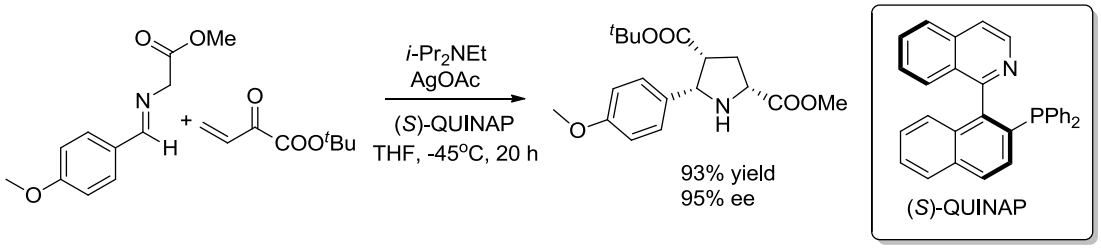


2.6 **Synthesis of α-Arylated Pyrrolidines and Tetrahydrofurans**:

Recently there have been reports on the synthesis of substituted or α-arylated pyrrolidines and tetrahydrofurans using multicomponent reactions. Most of them employ (3+2) cycloaddition or by functionalization of an established heterocyclic core. In contrast, strategies relying on cyclizing an acyclic precursor featuring all the requisite stereocenters remain less explored[49-52] owing to the challenges posed by acyclic stereocontrol.

In 2003, Schreiber reported catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides with electron-deficient olefins for the enantioselective synthesis of substituted proline derivatives.[53] The enantioselectivity was achieved using a chiral phosphine ligand (*S*)-QUINAP (Scheme 2.19).

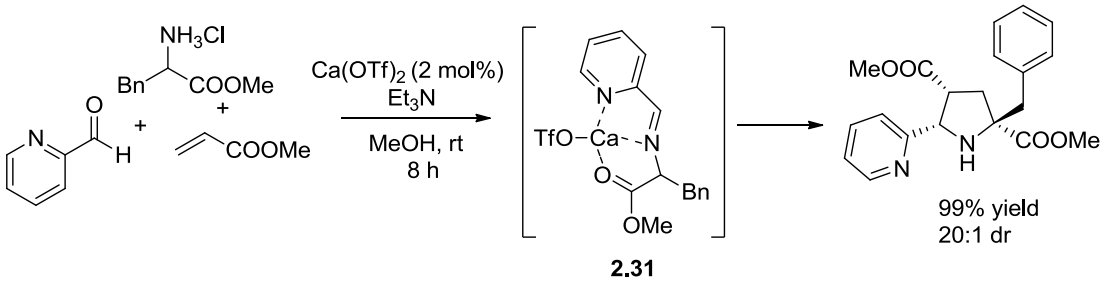
Scheme 2.19



As the methodology is developed using multicomponent reaction and due to its divergent nature, it is of considerable interest in diversity oriented synthesis (DOS).

Aron and coworkers in 2010 demonstrated the utility of multicomponent reaction in synthesis of pyrrolidines. They reported formation of azomethine ylide facilitated by metal chelation **2.31**, which upon diastereoselective (3+2) cycloaddition afforded tri and tetra-substituted pyrrolidines (Scheme 2.20).[54] Metal chelation stabilizes the dominant conformer of the reactant species and controls the diastereoselectivity in 1,3-dipolar cycloaddition reaction.

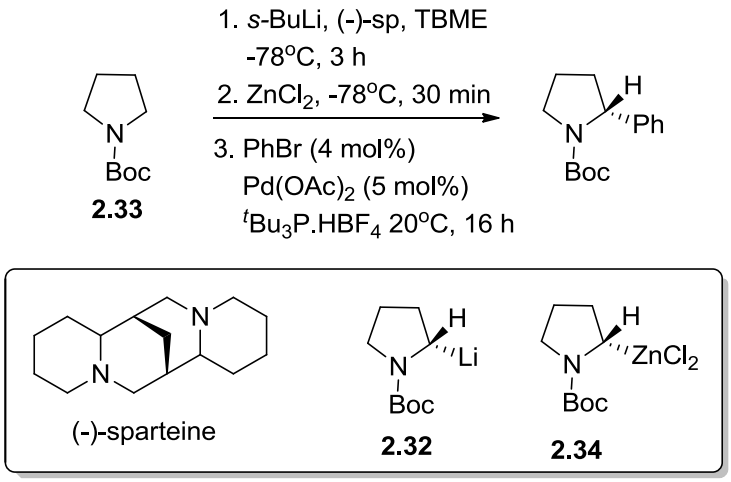
Scheme 2.20



2.31

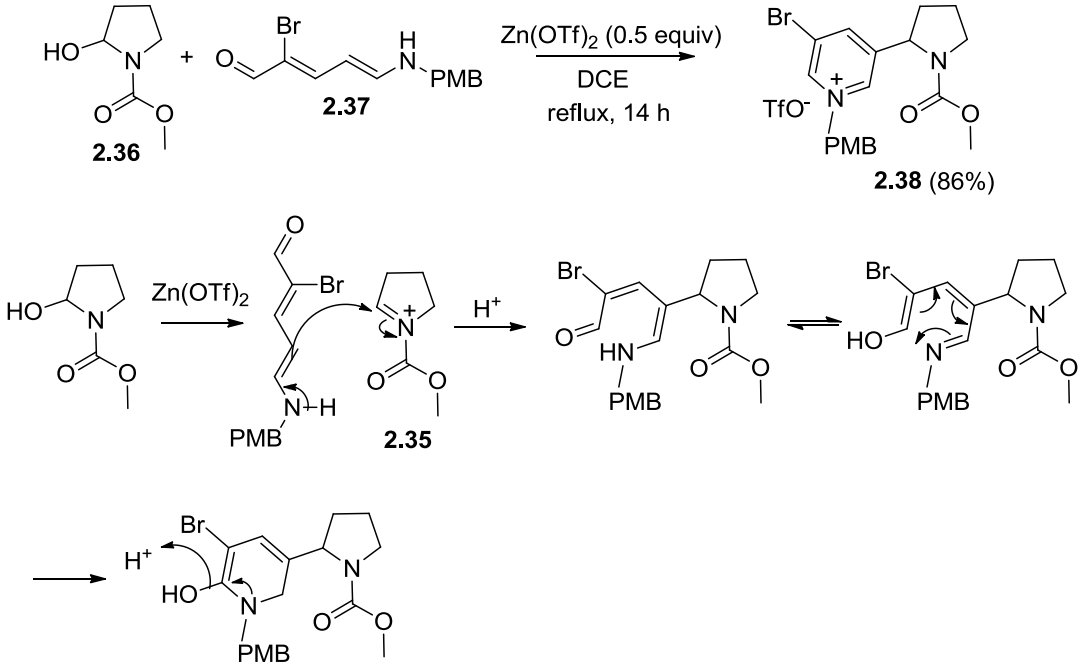
As mentioned earlier there are reports of α-arylation of pyrrolidines using a pre-functionalized heterocyclic precursor. O'Brien and coworkers in 2011 reported the directed metalation of pyrrolidines for the synthesis of α-arylated pyrrolidines (Scheme 2.21).[55] Access to organolithium reagent **2.32** was achieved using *s*-BuLi/ (-)-sparteine mediated asymmetric deprotonation of *N*-Boc pyrrolidine **2.33**. Transmetallation of the organolithium intermediate with $ZnCl_2$ affords **2.34** followed by a Pd-catalyzed Negishi coupling gave access to α-arylated pyrrolidines with good yield and enantioselectivity.

Scheme 2.21



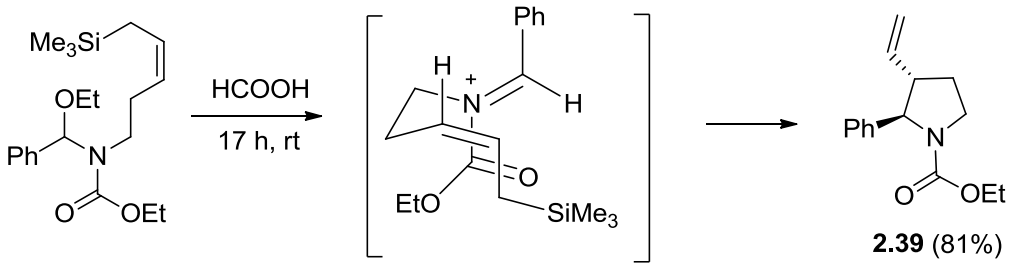
Using the concept of nucleophilic addition of enamine to cyclic *N*-acyliminium ion, Delpech and coworkers reported one-pot formation of α-pyridinium salt substituted piperidines and pyrrolidines (Scheme 2.22).[56] The *N*-acyliminium ions **2.35** were generated in situ from α-hydroxycarbamates **2.36** derived from pyrrolidine or piperidine, in the presence of zinc triflate. Nucleophilic addition of aminopentadienal **2.37** followed by a dehydrative cyclization afforded α-pyridinium salt substituted pyrrolidines **2.38**.

Scheme 2.22



There are few reports[57-58] involving ring closure of an acyclic precursor to synthesize α-arylated pyrrolidines. Hiemstra *et al.* reported an intramolecular cyclization of acyclic *N*-acyliminium ions with allyl silanes as nucleophiles to synthesize α-arylated vinyl pyrrolidines **2.39** (Scheme 2.23).[58]

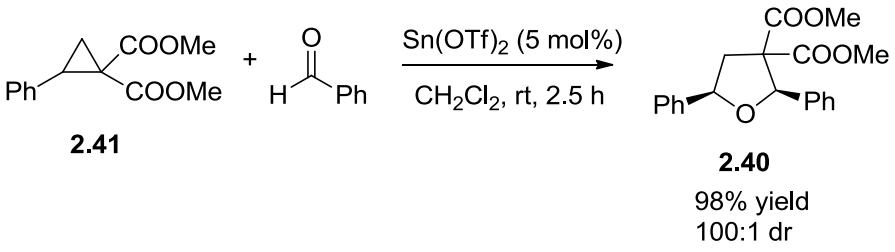
Scheme 2.23



Johnson *et al.* described an one-step diastereoselective synthesis of *cis*-2,5 disubstituted tetrahydrofurans **2.40** via Lewis acid catalyzed [3 + 2] cycloadditions of

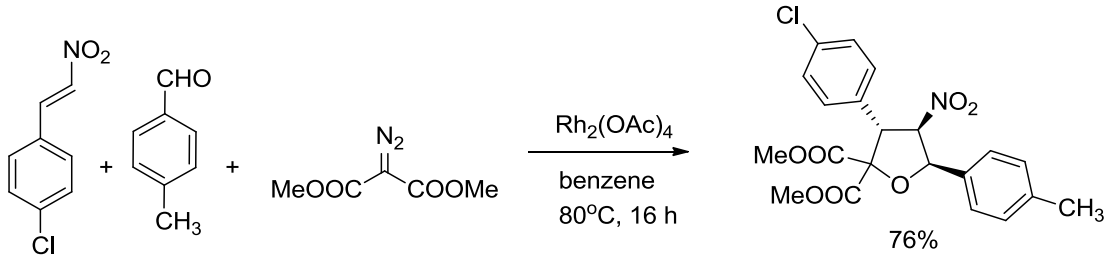
donor-acceptor cyclopropanes **2.41** and aldehydes (Scheme 2.24).[59] The methodology facilitates the stereospecific synthesis of a range of optically active tetrahydrofurans derivatives from enantioenriched donor acceptor cyclopropanes. The reaction proceeds with inversion at the cyclopropane donor site and allows absolute stereochemical information to be transferred to the products with high fidelity.

Scheme 2.24



Alternate approach to synthesis of substituted tetrahydrofurans was described by Nair[60] using Rh(II)-catalyzed reaction of dimethyl diazomalonate with aryl aldehydes and β-nitrostyrenes (Scheme 2.25). The reaction afforded diversely substituted tetrahydrofurans.

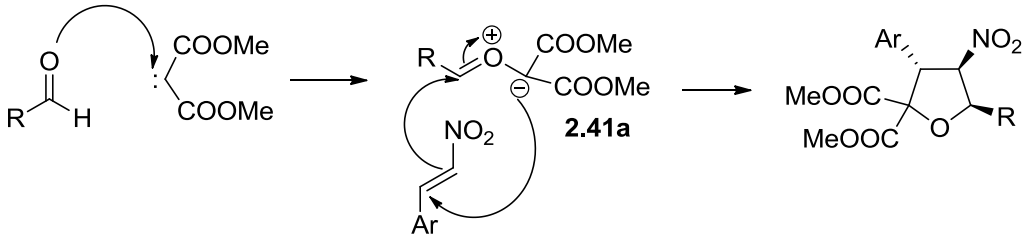
Scheme 2.25



Mechanistically the reaction may be considered to involve the dipolar cycloaddition of the carbonyl ylide **2.41a** formed by the reaction of the carbene and the aldehyde, to

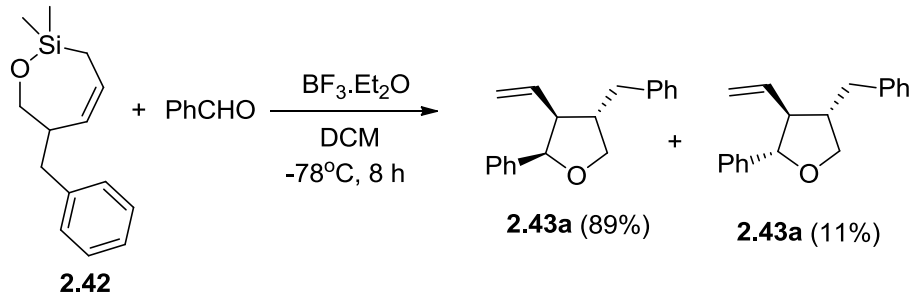
the β-nitrostyrene, the latter being a very good dipolarophile (Scheme 2.26). The diastereoselectivity of the reaction may be rationalized by the concerted nature of the carbonyl ylide cycloaddition and the observed relative stereochemistry of the products may be attributed to the preferred *trans* geometry of the ylide and the dipolarophile.

Scheme 2.26



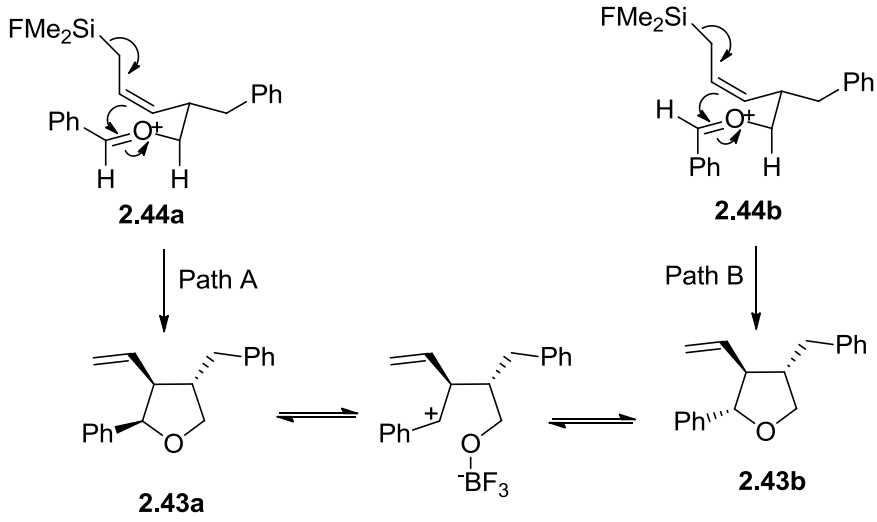
Marsden and coworkers reported[61] a reagent-controlled stereoselective synthesis of 2,3,4-trisubstituted tetrahydrofurans related to the furanolignan family of natural products (Scheme 2.27). Reaction of cyclic allylsiloxanes **2.42** with aldehydes in the presence of a Lewis acid produced tetrahydrofurans **2.43**. The reactions proceeded with complete 3,4-*trans* stereoselectivity, whereas the C-2 stereochemistry was determined by both the aldehyde and Lewis acid used.

Scheme 2.27



The predominant formation of 2,3-*cis*, 3,4-*trans* isomer **2.43a** can be rationalized by assuming that the reaction takes place by condensation of the siloxane oxygen with the aldehyde, leading to the formation of an (*E*)-oxonium ion **2.44a** which undergoes cyclization through a chair like transition state with all substituents equatorially disposed (path A, Scheme 2.28).

Scheme 2.28



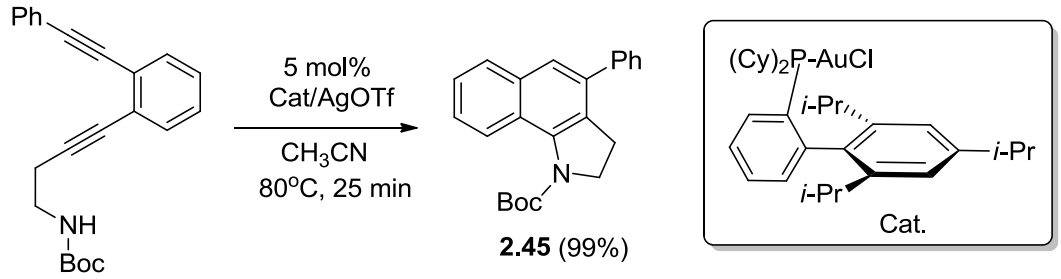
2.7 **Synthesis of Benzofused Heterocycles**:

Reports dedicated exclusively to synthesis of these heterocyclic cores are scarce. Some of the elegant approaches incorporating cascade and sequential reactions along with few classical routes to synthesize these heterocycles and heterocycles analogous to them will be discussed in this section.

Synthesis of benzoindoline **2.45** by gold-catalyzed cascade cyclization of diynes was reported by Fujii (Scheme 2.29).[62] This was achieved via an intramolecular gold-catalyzed cascade 5-*endo-dig* hydroamination followed by a 6-*endo-dig* cycloisomerization. Some of the indole analogs synthesized using this

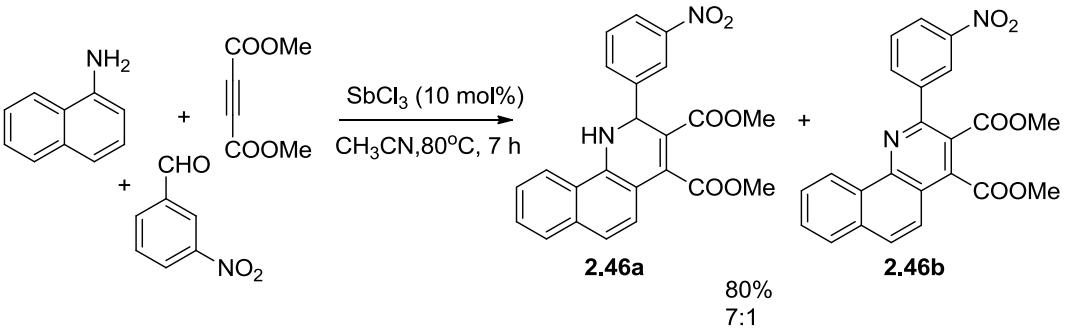
methodology exhibited good to excellent antifungal activities against *T. mentagrophytes* and *T. rubrum*, demonstrating the practical application of the cascade reaction for drug discovery, including the development of antifungal agents.

Scheme 2.29



Recently Maiti *et al.* reported a one-pot imino Diels–Alder reaction for the synthesis of dihydrobenzoquinoline **2.46a** derivatives catalyzed by antimony trichloride (Scheme 2.30).[63] The fully aromatized benzoquinoline **2.46b** was also formed as a minor product. Due to its operational simplicity, use of inexpensive catalyst, ease of product isolation, the author notes that the methodology is well suited for the library synthesis of dihydrobenzoquinoline derivatives.

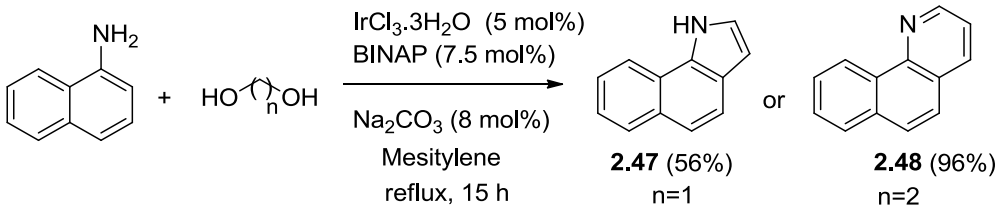
Scheme 2.30



Synthesis of fully aromatized analogs-benzoindoles **2.47** and benzoquinolines **2.48** was reported by Ishii *et al.*[64] It was achieved by *N*-heterocyclization of

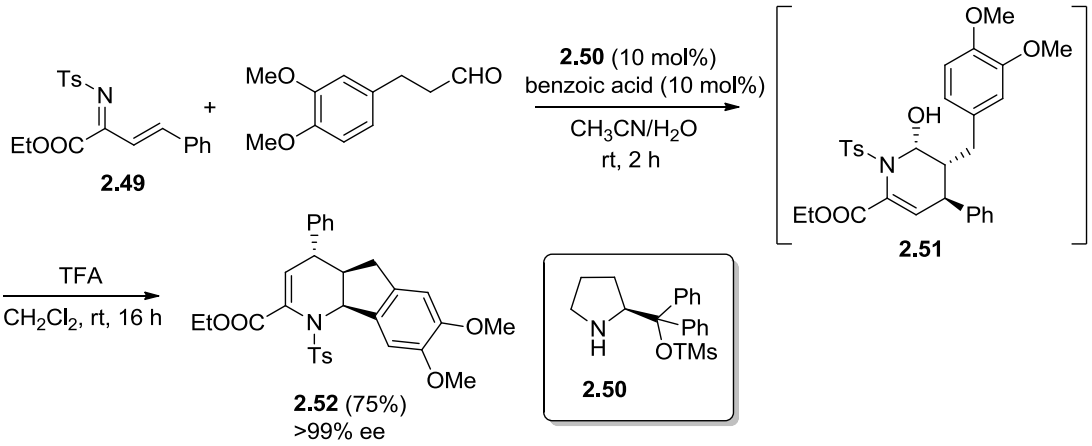
naphthylamines with 1,2- and 1,3-diols catalyzed by an iridium chloride/BINAP system (Scheme 2.31). The reaction was found to be markedly influenced by the ligands employed. No reaction occurred in the absence of ligand. Monodentate ligands afforded lower yields. Typical bidentate phosphine ligands such as 1,2-bis(diphenylphosphino) ethane (dppe) and 1,3-bis(diphenylphosphino) propane (dppp) were less efficient than monodentate. Finally *rac*-BINAP was found to be the efficient ligand.

Scheme 2.31



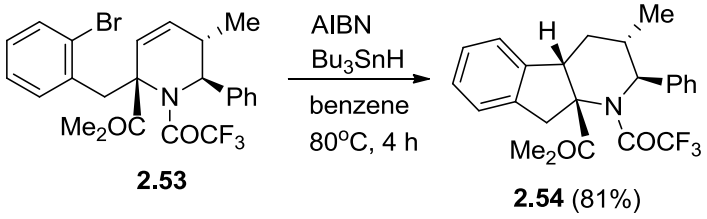
Using a sequential hetero-Diels-Alder/Friedel-Crafts reaction, Chen *et al.* demonstrated a highly enantioselective synthesis of analogs of indeno dihydropyridines **2.52** (Scheme 2.32).[65] The methodology relies on the chiral secondary amine-catalyzed aza-Diels-Alder of *N*-sulfonyl-1-aza-1,3-butadienes **2.49** and aliphatic aldehydes via enamine catalysis using α,α-diphenylprolinol *O*-TMS ether **2.50**. A subsequent intramolecular Friedel-Crafts reaction of the hemiaminal **2.51** functional group with a tethered arene motif in the presence of TFA delivers analogs of indenodihydropyridine **2.52**.

Scheme 2.32



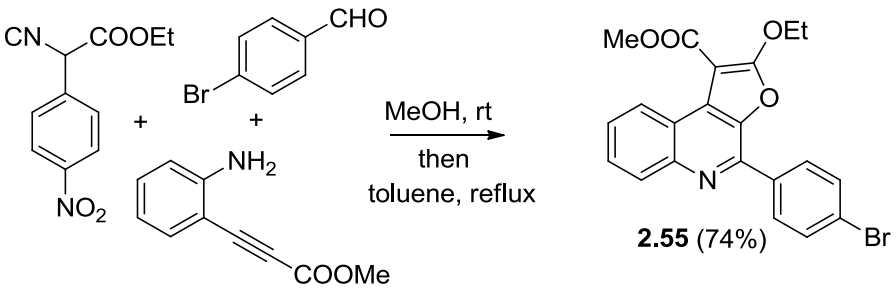
Panek and Porco reported[66] synthesis of indenopiperidine via radical cyclization of suitably functionalized tetrahydropyridine **2.53**. Treatment of the substrate with tributyltin hydride in the presence of a catalytic amount of AIBN at 80°C, cleanly afforded the indenopiperidine **2.54** in 81% isolated yield (Scheme 2.33).

Scheme 2.33



Exploiting the divergent reactivity of isocyanoacetates, Masson *et al.* reported[67] three-component synthesis of furoquinolines **2.55** (Scheme 2.34). It is interesting to note that no external reagent was required and heating was the only external force needed to promote this mechanistically complex reaction that led to the creation of five chemical bonds and two heterocyclic rings.

Scheme 2.34



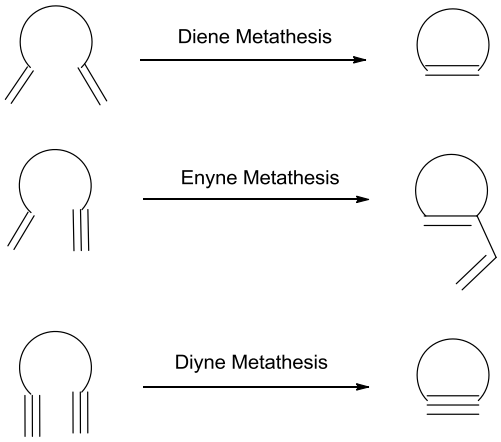
The operational simplicity and good chemical yields makes this novel heterocycle synthesis appealing in diversity-oriented synthesis.

Part III

Ring Closing Enyne Metathesis

Ring closing metathesis reactions can are classified into three categories depending on the interacting partners i.e., diene,[68] enyne[69] and diyne[70] metathesis (Figure 2.3). These reactions can be further sub-divided into ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP) and cross metathesis (CM), based on the process that occurs during the reaction. Through these reactions, olefin metathesis provides a route to unsaturated molecules that are often challenging or impossible to prepare by any other means. Some of the most impressive achievements include the use of ROMP to make functionalized polymers,[71-72] syntheses of small to large heterocyclic systems by RCM[73-74] and the CM of olefins with pendant functional groups.[75-76] Moreover the approach of natural product synthesis has changed after the advent of RCM.[77]

Figure 2.3



Ring-closing enyne metathesis, as the name suggests is a rearrangement that occurs between a double and a triple bond. It is completely atom economical.[78] During the course of this reaction, the terminal alkylidene moiety of alkene transfers on the

alkyne carbon and a new bond formation occurs between alkynic and olefinic carbons providing a cyclized product with a 1,3-diene moiety.[69] Intermolecular enyne metathesis reactions lead to the formation of several products like olefins and polymers in addition to the desired diene. This is because; there are two types of metathesis occurring in addition to the intermolecular enyne metathesis. They are intermolecular diene metathesis and intermolecular alkyne metathesis. The catalyst can further react with these byproducts to provide complex mixture. Therefore intramolecular enyne metathesis is more popular than intermolecular enyne metathesis and widely used in synthetic organic chemistry.

2.7 **Catalysts for Olefin metathesis (OM)**:

Transition metal carbenes have been used to catalyze metathesis reactions. Initially, tungsten, molybdenum and chromium carbenes were used as catalysts.[26, 79] The chemoselectivity of the catalysts employed in olefin metathesis is important. They have to react selectively with the olefin in the presence of other functional groups either in the substrate or the solvent. Being an oxophilic metal, tungsten was extremely sensitive to a number of functional groups and reaction conditions. Schrock developed[80] molybdenum-based catalysts that exhibited a larger functional group tolerance allowing OM to become a viable tool for organic syntheses.[81] Unfortunately, manipulation of Mo-based catalysts still required stringent air-free and water/alcohol-free conditions. Low functional group tolerance and instability have limited the application of these metathesis catalysts. A very small amount of active

form is generated from these catalysts and therefore, these reactions were difficult to initiate and to control.

However, after the discovery of a ruthenium alkylidene catalyst by Grubbs, many of the problems encountered with previous catalysts were eliminated. OM process truly became a versatile tool for organic synthesis and polymer synthesis.[82] Prof. Robert H. Grubbs was awarded Nobel Prize for chemistry in 2005, shared with Prof. Richard R. Schrock and Prof. Yves Chauvin, for the contribution to the metathesis chemistry.

The functional group tolerance of metal carbenes increases from titanium < tungsten < molybdenum < ruthenium (Table 2.2) shows the tremendous functional group tolerance of ruthenium based catalysts compared to previous metathesis catalysts. In the table below, carbenes can tolerate only the functional groups listed underneath the olefins.[26]

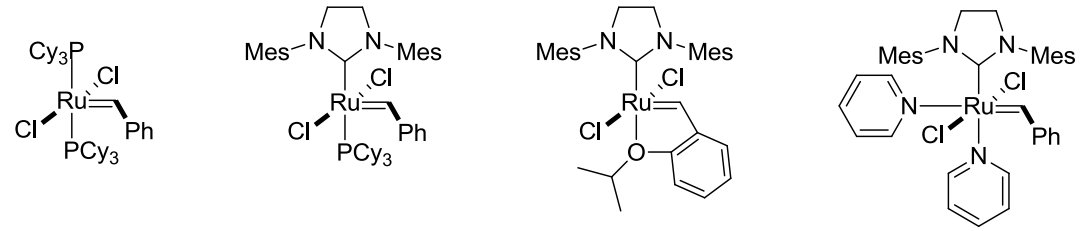
Table 2.2: *Functional tolerance of transition metal carbenes*

Titanium	Tungsten	Molybdenum	Ruthenium
Acids	Acids	Acids	**Olefins**
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	**Olefins**	Aldehydes
Esters, Amides	**Olefins**	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides

The most commonly used Grubbs catalysts are the 1st generation catalyst (**cat-I**)[83] and the 2nd generation catalyst (**cat-II**)[84](Figure 2.4). The latter, which is a *N*-

heterocyclic carbene (NHC)-coordinated ruthenium benzylidene complex, has higher activity and air stability compared to the 1st generation. The presence of *N*-heterocyclic carbene is the cause for these differences. This catalyst has been used for a broad range of reactions including metathesis of sterically demanding substrates[76, 85-86] and electron-deficient substrates.[87-89] Hoveyda[90] and Blechert[91] independently developed a phosphine free Ru catalyst (**cat-III**). This catalyst is widely used for ring-closing metathesis of trisubstituted olefins and in cross metathesis processes. Recently, Grubbs introduced the third generation catalyst (**cat-IV**) which is synthesized by replacing the phosphine ligand in cat-II with a more labile pyridine ligand. Rapid dissociation of electron deficient 3-bromopyridine ligand and/or its slow rebinding has been postulated to account for this higher activity. This catalyst is most widely used in ROMP and CM of acrylonitrile.[92]

Figure 2.4



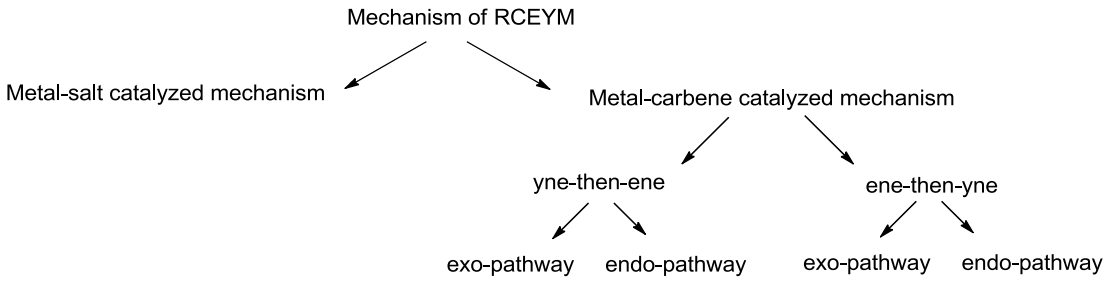
Grubbs 1st Gen **cat-I**

Grubbs 2nd Gen **cat-II**

Grubbs-Hoveyda **cat-III**

Grubbs 3rd Gen **cat-IV**

2.9 **Overview of Mechanism of Ring Closing Enyne Metathesis**:

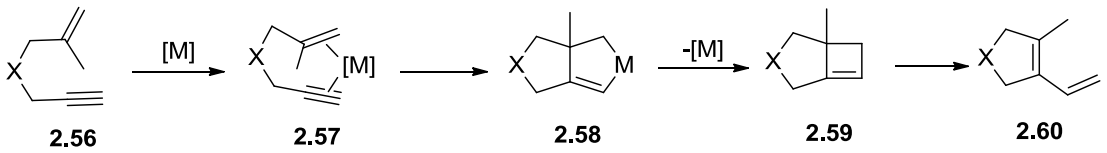


Two types of mechanisms are proposed for enyne metathesis.[93]

i) *Metal-salt catalyzed mechanism:*

According to this mechanism (Scheme 2.35), first step is the bidentate coordination of the substrate-**2.56** via the ene and yne component to the metal to form complex-**2.57**. Oxidative cyclization followed by reductive elimination produces cyclobutene intermediate-**2.59**. Finally the retrocyclization/ring opening of cyclobutene affords desired 1,3-diene product-**2.60**.

Scheme 2.35



Mostly Pd(II) and Pt salts have been used for enyne bond reorganization.[94]

ii) *Metal-carbene catalyzed mechanism:*

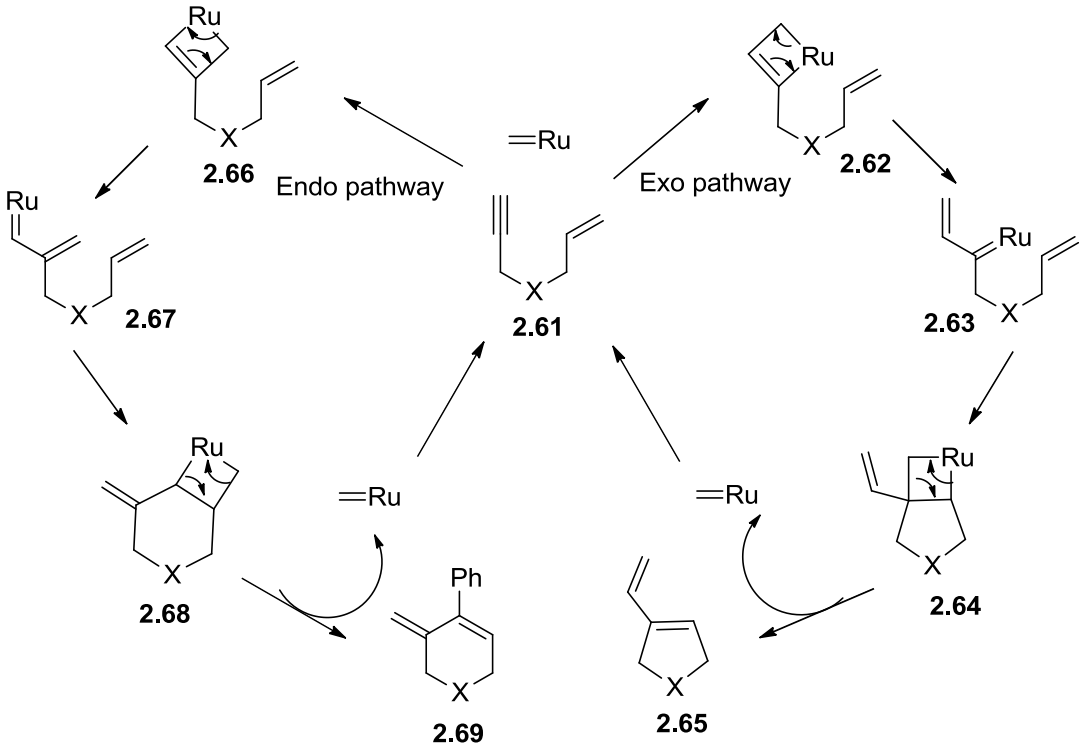
This mechanism is sub-divided into two categories depending on the initial coordination of the substrate on to the metal.

iia) *Yne-then-ene mechanism*:

Here the alkynyl moiety of the substrate **2.61** coordinates first to the ruthenium-carbene complex. Depending on the regiochemistry of this coordination, the mechanism is further classified as "*exo*-pathway" and "*endo*-pathway".[93] If the metal combines with the internal alkynyl carbon of the alkyne motif, then it proceeds via the *exo*-pathway. The coordination affords a ruthenacyclobutene **2.62** which upon ring opening forms a vinylic ruthenium carbene complex **2.63**. An intramolecular [2+2] cycloaddition of **2.63** gives rise to ruthenacyclobutane **2.64** and a retrocyclization affords product **2.65**.

The "*endo*-pathway" can be observed when the metal coordinates to the terminal alkynyl carbon. Similar to the *exo*-pathway, the coordination affords a ruthenacyclobutene **2.66** which upon ring opening yields a vinylic ruthenium carbene complex **2.67**. An intramolecular [2+2] cycloaddition forms ruthenacyclobutane **2.68** and a cycloreversion delivers product **2.69**. Regeneration of ruthenium carbene complex occurs in both the pathways (Scheme 2.36).

Scheme 2.36



iib) *Ene-then-yne mechanism*:

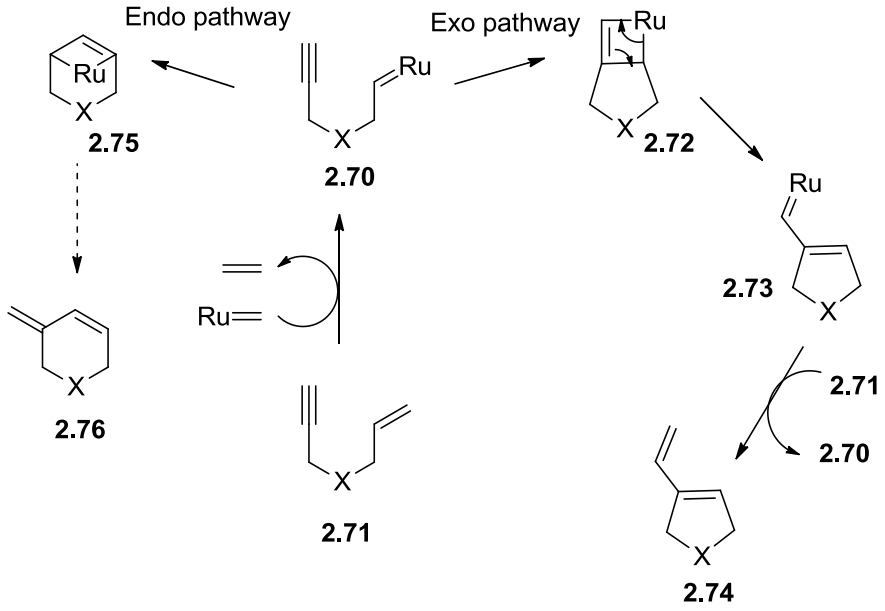
In this route the alkene moiety of the substrate coordinates first to the ruthenium carbene complex.[93] The mechanism is further classified as the *exo*-pathway and *endo*-pathway, depending on the regiochemistry of the coordination of ruthenium alkylidene complex to the alkyne. Complex **2.70** is formed by the reaction between substrate **2.71** and the catalyst =Ru (Scheme 2.37).

In *exo*-pathway the ruthenium in complex **2.70** coordinates with terminal carbon of the alkyne and undergoes ring closure to form ruthenacyclobutene **2.72**. Retrocyclization yields vinylic ruthenium carbene complex **2.73** which reacts with the

second equivalent enyne substrate **2.71** to regenerate the complex **2.70** and the product **2.74**.

Alternatively, the *endo*-pathway produces strained ruthenocyclobutene **2.75**, by the combination of the ruthenium metal center in **2.70** with the internal alkynyl carbon. Finally product **2.76** is obtained by the ring opening of ruthenocyclobutene. Since the intermediate **2.75** is unstable due to its high strain, it is expected that obtaining the *endo*-product from this mechanism is quite unlikely.

Scheme 2.37



There are examples of yne-then-ene mechanism as noted by Mori etal.[95] It is explained that this is due to the higher reaction rate of the ruthenium-carbene with the alkyne moiety compared to that with the olefin moiety. On the other hand; Hoye, based on the NMR studies, favored the *ene*-then-*yne* mechanism for RCEYM.[96] He suggests that substrate concentration has an influence on the mechanism and it is

beneficial to have a higher substrate and lower ruthenium carbene concentration for reactions that follow this pathway. It can be achieved by the slow addition of ruthenium carbene to the solution of substrate.

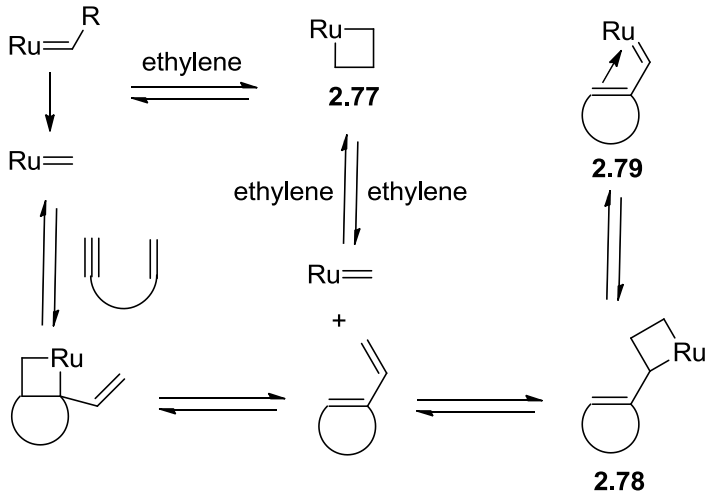
The *exo*/*endo* selectivity is another important aspect of the enyne methathesis mechanism as it controls the ring size of the resulting product. It has been shown that for small ring formation (ring size = 5-9) *exo*-pathway is favored while formation of macrocycles (ring size = 11-15) desires the *endo*-pathway.[97] This outcome can be explained by the *ene*-then-*yne* mechanism, considering the ring strains of ruthenocyclobutene intermediates.[69] When the length of the tether increases, the strain of the *endo*-intermediate is reduced considerably and thus could provide an explanation for these observations. But this cannot be easily explained for the *yne*-then-*ene* mechanism and the switch between *exo*/*endo* selectivity is still not clear. Potentially the steric and conformation of the tether could play a vital role.

2.10 **Effect of Ethylene Gas in Enyne Metathesis**:

In some of the challenging enyne metathesis reactions, the yield was improved when they were performed under the ethylene atmosphere.[98-100] Mechanistically the activity increase in the presence of ethylene is explained by a constant 'reactivation' of the ruthenium catalyst and thereby reducing amount of catalyst in resting state.

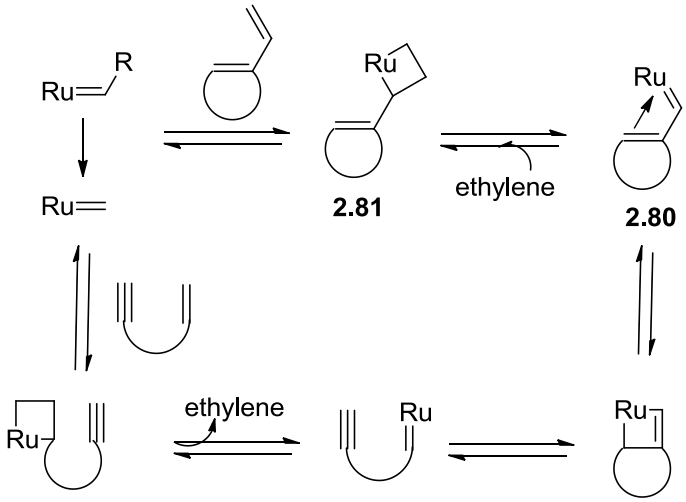
During *yne*-then-*ene* pathway (Scheme 2.38) the ethylene forms ruthenacyclobutane **2.77** with active ruthenium alkylidene. This helps the reaction push forward and prevents the ruthenium catalyst being trapped in less active species **2.78** and **2.79** formed due to reaction between the product and ruthenium alkylidenes.

Scheme 2.38



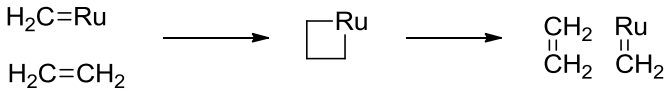
In the course of *ene*-then-*yne* pathway (Scheme 2.39), the less active species **2.80** would be formed. Ethylene reacts with **2.80** to form ruthenacyclobutane **2.81** and thus pushes the reaction forward.

Scheme 2.39



Another important point to know is that the self-metathesis of ethylene is a neutral process and does not affect the progress of reaction (Scheme 2.40).

Scheme 2.40



The benefits of ethylene atmosphere appear to be general in RCEYM reactions forming small to medium sized ring systems. But in formation of large membered rings, the use of ethylene can lead to CM products with starting materials.[69, 97] This could be attributed to relatively slower rate of macrocyclization via enyne metathesis.

Part IV

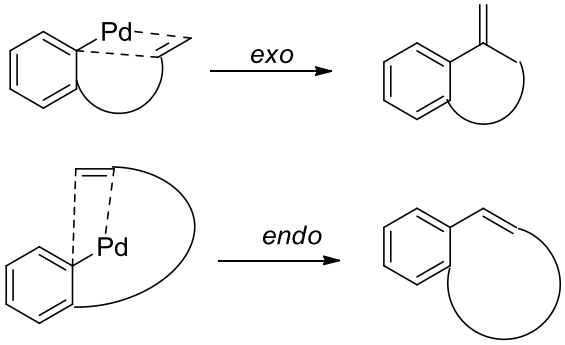
Regiocontrol in Intramolecular Heck Cyclization

A significant challenge in the development of metal-catalyzed reactions is the suppression of competing mechanistic pathways without inhibiting desired steps in a catalytic cycle.[101-102] In recent years, several remarkable transformations have been effected through the use of palladium catalysts that minimize side reactions (e.g., β-hydride elimination) while still allowing reductive elimination or transmetalation processes to occur.[103-106] Despite these achievements, the factors that affect the relative rates of competing mechanistic pathways in catalytic reactions (e.g., reductive elimination versus olefin insertion, or C-C versus C-N bond-forming reductive elimination) are not well understood. If these fundamental processes could be controlled, the selective construction of a diverse array of products from common starting materials could be achieved under similar reaction conditions by varying catalyst structure.

2.11 **Factors Controlling Competing Pathways: 5-*exo*- versus 6-*endo* Cyclization in Intramolecular Heck Cyclization**

The intramolecular Heck reaction often proceeds with high regio- and stereoselectivity when compared to intermolecular Heck reaction. This is mainly dependent on the reaction conditions and the ring size of the heterocycles formed; with *exo* being particularly favored for 5, 6 and 7 membered rings due to conformational constraints.[107-109] The transition state to form *exo* products, in reactions forming small rings is much lower in energy than the *endo* transition state due to length of the tether. Much longer and more flexible chains are needed to adopt the proper conformation of the *endo* insertion (Figure 2.5).

Figure 2.5

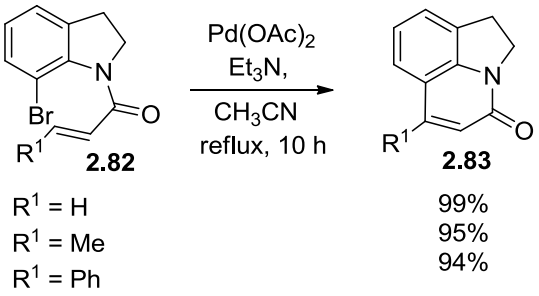


The 5-*endo*-trig and 6-*endo*-trig cyclizations are not very common; this circumstance is usually rationalized by Baldwin's rules.[110] Baldwin's rules in organic chemistry are a series of guidelines outlining the relative feasibilities of ring closure reactions in alicyclic compounds. Apart from Baldwin's rules, some of the other factors which control the competing pathways in an intramolecular Heck cyclization are discussed in the following sections.

2.11.1 **Steric and Conformational Effects in the Substrate**:

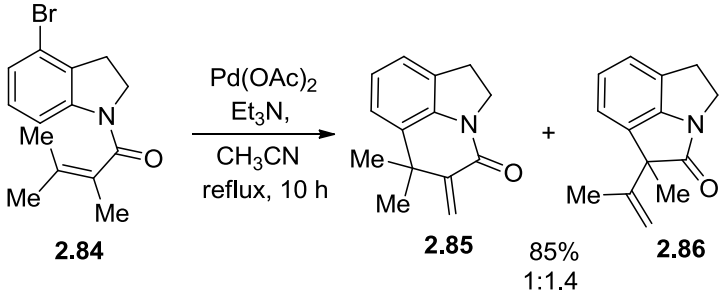
Dankwardt *et al.* reported[111] that *N*-acryloyl-7-bromoindolines **2.82**, which possibly could cyclize via either the 5-*exo* or 6-*endo* pathway, furnished exclusively 6-*endo* products when treated under typical Heck reaction conditions (Scheme 2.41). The cyclization of acrylamides proceeded efficiently to give quinolone products **2.83** via 6-*endo*-trig cylization.

Scheme 2.41



However, it was found that the corresponding cyclization of tetrasubstituted amide **2.84** attempted under the same conditions provided a mixture of compounds **2.85** and **2.86** in a 1:1.4 ratio respectively (Scheme 2.42). Also this cyclization reaction proceeded slower than the previous cases (substrates **2.82**) presumably due to increased steric hindrance.

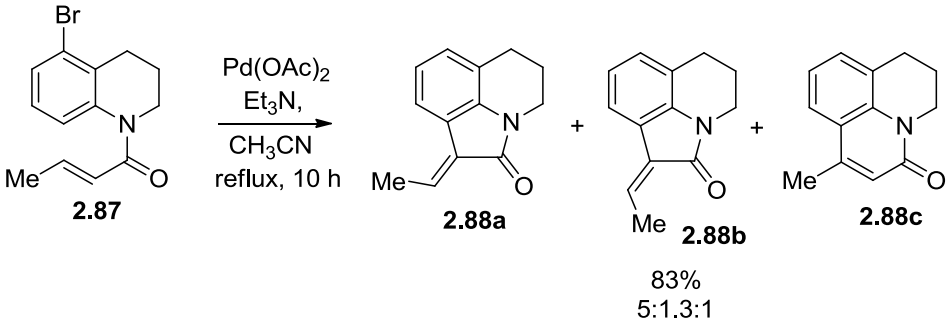
Scheme 2.42



The author explains that the palladium-catalyzed cyclization of **2.82** through a 6-*endo* pathway is presumably due to strain involved in the approach of the palladium species to the α position of the double bond of these acrylamides, thus generally disfavoring the 5-*exo*-trig mode of closure.

In order to probe the effect of ring size on the regiochemistry of cyclization, amide **2.87** was subjected to the palladium cyclization conditions (Scheme 2.43).

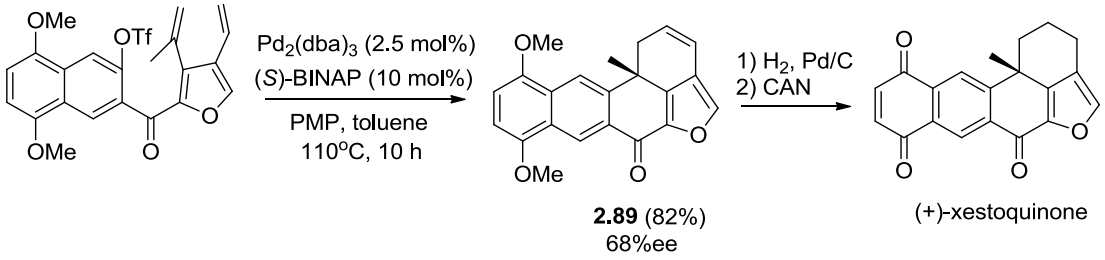
Scheme 2.43



The reaction afforded lactams **2.88a**, **2.88b** and **2.88c** in a 5:1.3:1 mixture. Thus a 6.3:l mixture of products favoring the 5-*exo*-trig pathway dominated in the reaction mixture. This result when compared to the reaction of indoline **2.82** (R^1=Me) affording exclusively **2.83** (R^1=Me) via 6-*endo* pathway, clearly depicts the effect of substrate ring conformation on the outcome of regiochemistry in Heck cyclization.

An enantioselective total synthesis of (+)-xesoquinone was developed by the Keay group using an asymmetric double Heck reaction (Scheme 2.44).[112] The reaction produced **2.89** in 82% yield and 68% of enantiomeric excess.

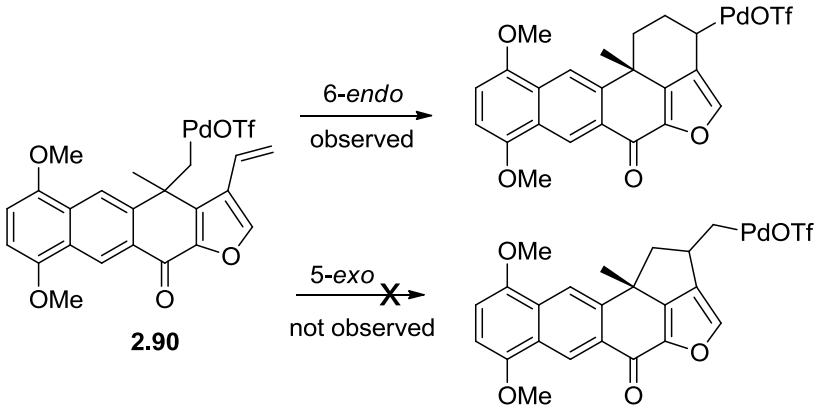
Scheme 2.44



In the second Heck reaction (Scheme 2.45), 6-*endo*-trig cyclization of the intermediate **2.90** was observed to give a six-membered ring instead of the seemingly more favored *exo*-trig cyclization, which would form five-membered ring. Density

function theory calculations by Ziegler and coworkers[113] revealed that this selectivity, at both thermodynamic and kinetic levels, is controlled by the stability of the cyclic system after the migratory insertion of the palladium into the exocyclic double bond.

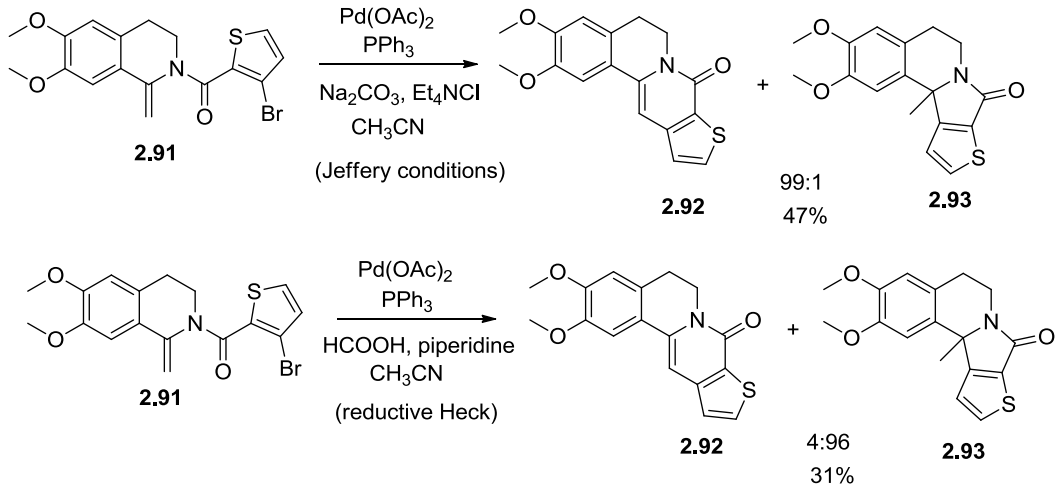
Scheme 2.45



2.11.2 **Catalysts and Reaction Conditions**:

An interesting case of 6-*endo* versus 5-*exo* cyclization has been studied by Bombrun and Sageot who investigated the intramolecular Heck cyclization of enamide **2.91** (Scheme 2.46).[114] Under Jeffery conditions the reaction proceeded nearly exclusively via the 6-*endo* cyclization mode to form piperidone fused product **2.92**. However when run under the reductive Heck conditions (in presence of hydride source), a 5-*exo* cyclization was mostly achieved and the lack of β–hydrogen in this case leads to pyrrolidinone fused product **2.93**.

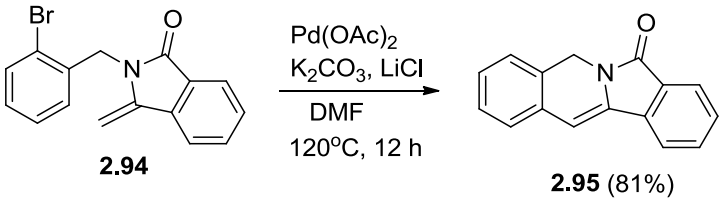
Scheme 2.46



Mechanistically both the reactions would undergo kinetically controlled 5-*exo* cyclization, to begin with. In the case of Jeffery conditions reaction, due to lack of β–hydrogen as well as due to absence of any nucleophile to terminate the reaction the 5-*exo* route happens to be the dead end. So the reaction reverses and proceeds via the thermodynamically controlled 6-*endo* pathway. In contrast, under reductive Heck condition due to presence of the hydride anion (nucleophile) the reaction can successfully terminate the 5-*exo* pathway and regenerate the catalyst for the new catalytic cycle.

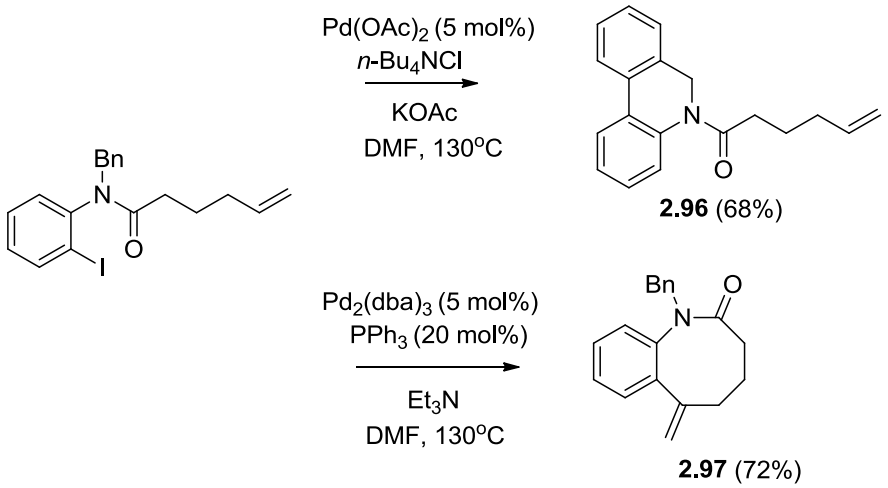
Another example giving exclusively 6-*endo* cyclized product was reported by Kim *et al.*[115] The cyclization of methylenephtalimidine precursor **2.94** afforded tetracyclic amide **2.95** under the ligandless Heck condtion (Scheme 2.47).

Scheme 2.47



The influence of 'ligand' and 'ligandless' conditions on the regioselectivity of Heck cyclization was reported by Hii *et al.* (Scheme 2.48).[116] The reaction was found to be highly dependent on the catalytic conditions, particularly the nature and presence and absence of the ligand. Biaryl coupled product **2.96** was preferred over 8-*exo* cyclization under "ligandless" conditions, whereas eight membered heterocycles **2.97** formed via 8-*exo* cyclization was the exclusive product using PPh_3 ligand.

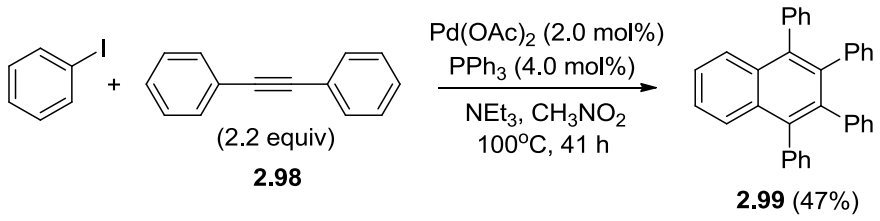
Scheme 2.48



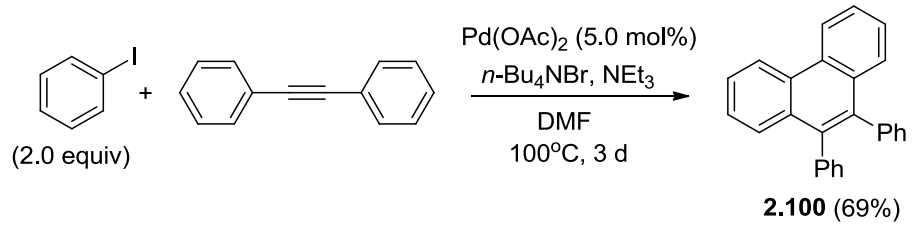
The remarkable effect that minor change in reaction conditions and substrate composition can have on the outcome of a palladium-catalyzed transformation is very well illustrated in the following examples. The Heck group described[117] the

palladium-catalyzed reaction of iodobenzene and twofold excess of tolane **2.98** in the presence of triphenylphosphine and triethylamine to give the substituted naphthalene **2.99** (Scheme 2.49). Dyker and Kellner[118] obtained the phenanthrene **2.100** when using a 2:1 mixture of iodobenzene and tolane in the presence of *n*-Bu_4NBr and K_2CO_3 (Scheme 2.50). Furthermore, Cacchi's group[119] employed almost identical conditions but added formic acid, which led to the formation of triphenylethene **2.101** (Scheme 2.51). Moreover, Larock and Tian[120] have recently reported an efficient synthesis of fluorenes **2.102**, again using iodobenzene and tolane as substrates (Scheme 2.52).

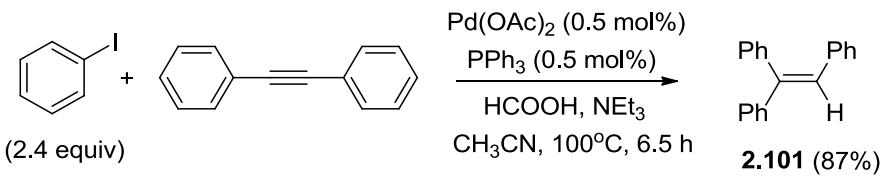
Scheme 2.49



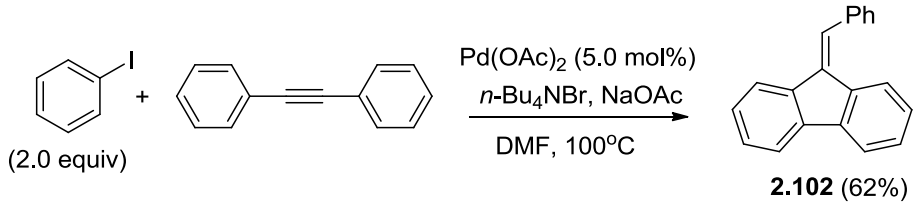
Scheme 2.50



Scheme 2.51



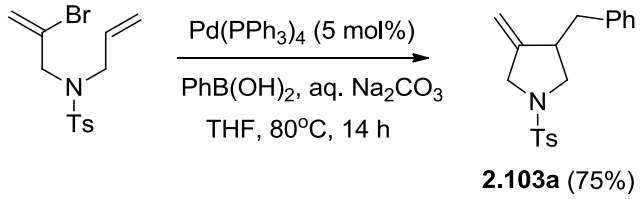
Scheme 2.52



2.11.3 **Suppression of a Pathway via Chelation**:

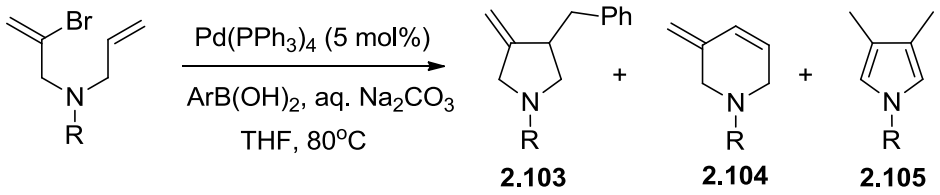
Suppression of competing β-hydride elimination is important especially in metal-catalyzed cross-coupling reactions. Kim and Ahn[101] have reported a sequential Heck-cyclization-Suzuki coupling that provides an efficient synthetic access to 4-methylene-3-arylmethylpyrrolidine **2.103a** (Scheme 2.53).

Scheme 2.53



However, studies on the scope of this sequence revealed that the substrate had to be an *N*-tosyl sulfonamide and that certain boronic acids did not transmetalate but rather gave rise to the formation of pyrrole **2.104** or a pyridine **2.105** derivative (Table 2.3)

Table 2.3

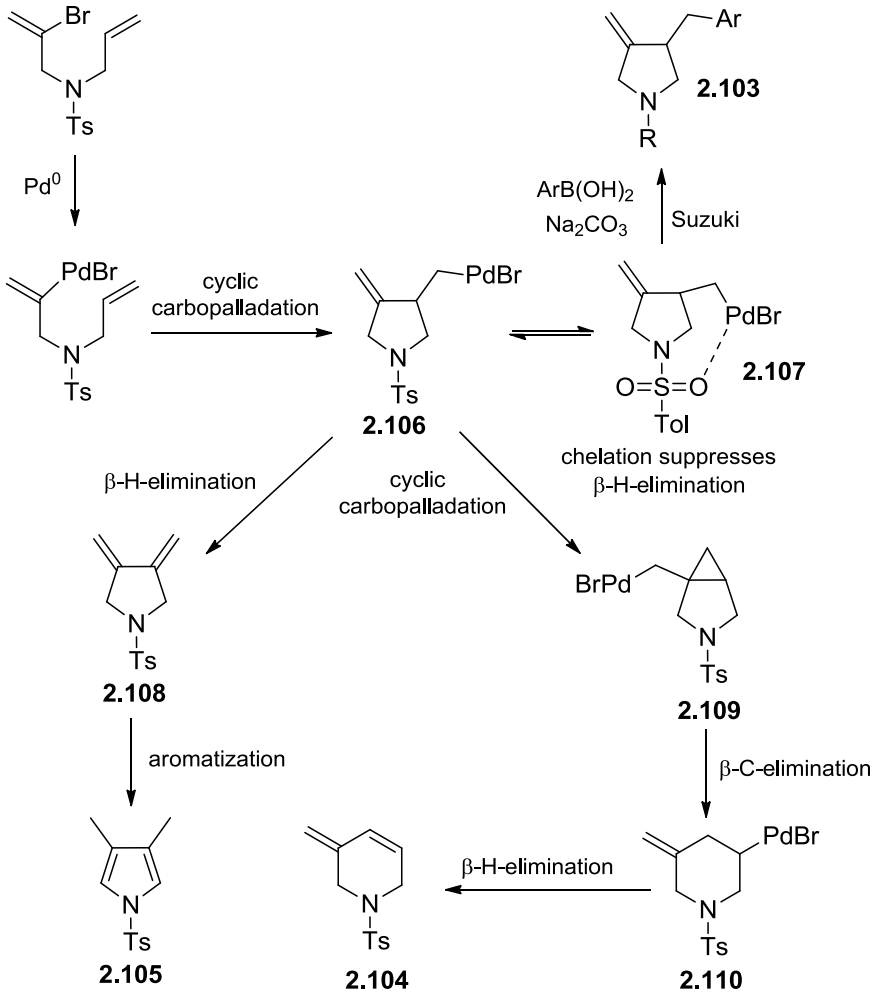


Entry	Substrate	$ArB(OH)_2$	Product	Yield (%)[a]
1	R=Ts	4-fluorophenylboronic acid	2.103	92
2		1-napthylboronic acid	2.103	88
3		3-nitrophenylboronic acid	2.103	49
4		2-furanboronic acid	2.104+2.105	26[b](58)
5		ferroceneboronic acid	2.104+2.105	61[c](19)
6	R=Bn	4-fluorophenylboronic acid	2.103	30
7	R=Ac	*n*-butylboronic acid	-	(69)
8	R=Boc	phenylboronic acid	-	-

[a]Yield in parenthesis indicates that of recovered starting material, [b]b/c= 3.3/1,[c]b/c=3.2/1

The peculiar outcome of carbopalladation-Suzuki sequence was rationalized by coordinative stabilization of the insertion intermediate **2.106** by the sulfonyl oxygen atom, as represented in structure **2.107**, thus suppressing the usual β-hydride elimination (Scheme 2.54).

Scheme 2.54

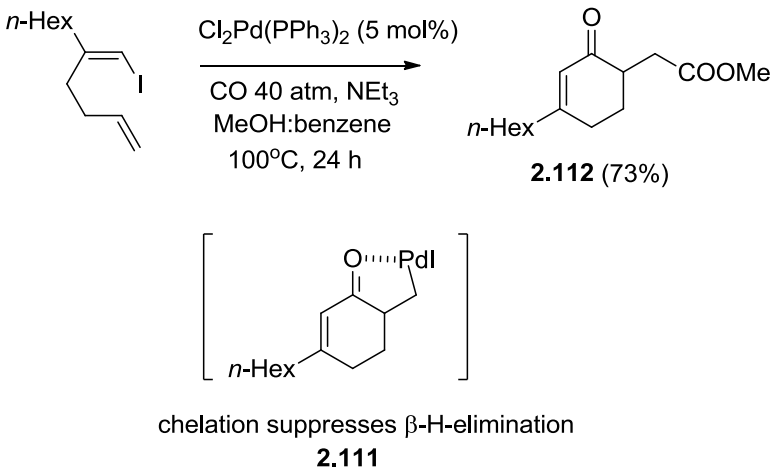


If the transmetallation is rapid the Suzuki product **2.103** is obtained. However if the transmetallation is slow, as for furyl or ferrocene boronic acids (entries 4 and 5), either β-hydride elimination or a subsequent cyclic carbopalladation occurs. The β-hydride elimination of **2.106** leads to the formation of the diene **2.108** that is isomerized to the pyrrole **2.105**. The carbopalladation of **2.106** furnishes the cyclopropylmethyl Pd species **2.109**, which rearranges with concomitant ring

expansion via β-carbon elimination to furnish piperidyl-Pd intermediate **2.110** that suffers β-hydride elimination to afford the methylene tetrahydro pyridine **2.104**.

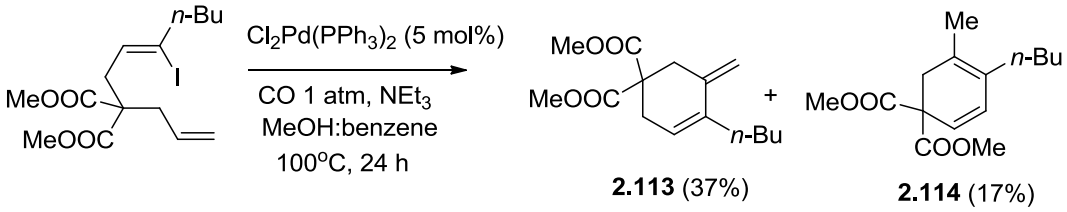
Negishi reported[102] a palladium-catalyzed carbonylative cyclization in which the β-H-elimination was suppressed under higher CO pressure (Scheme 2.55). It was suggested that an adjacent carbonyl oxygen atom coordinatively stabilizes an alkylpalladium intermediate. Fast CO insertion is also considered to be a contributing factor to the success of the process, which proceeds prior to the decomposition of the alkylpalladium intermediate.

Scheme 2.55



Under the higher CO pressure, the initial carbonylation generates cyclohexenone intermediate which coordinatively stabilizes the putative alkylpalladium **2.111**. The latter upon carbonylation and methanolysis furnished observed product **2.112**. Under lower or in absence of CO atmosphere the reaction followed normal Heck pathway of carbopalladation followed by either β-H-elimination or isomerization to afford dienes **2.113** and **2.114** respectively (Scheme 2.56)

Scheme 2.56

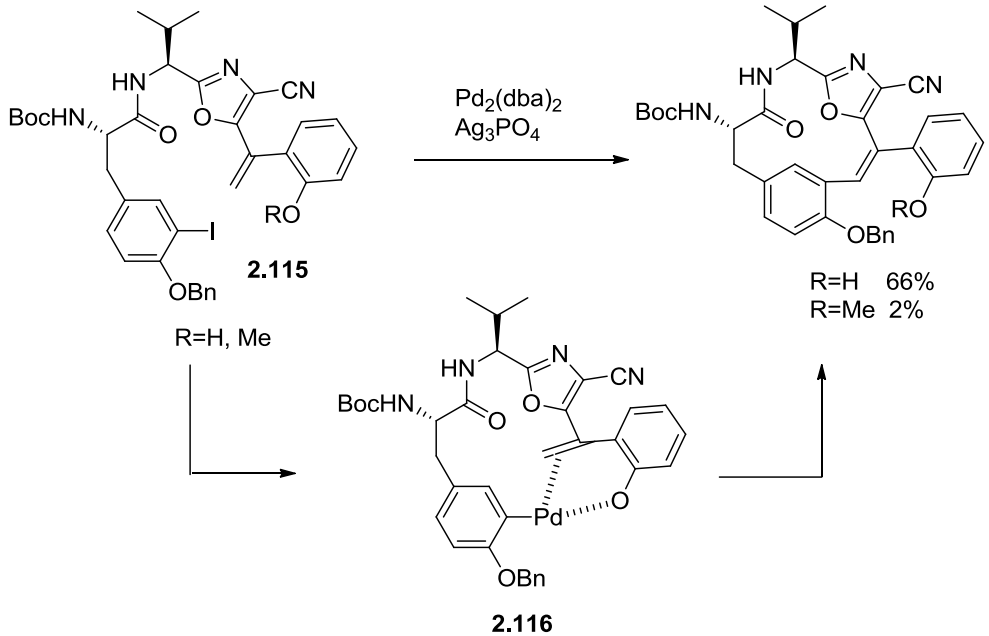


2.113 (37%) **2.114** (17%)

2.11.4 **Chelation Driven Heck Cyclization**:

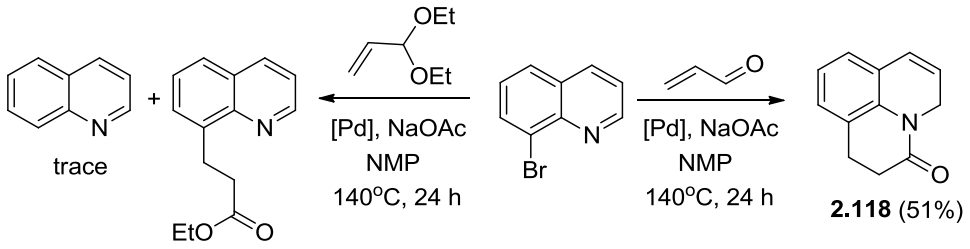
Harran and coworkers reported[121] an interesting example of Heck macrocyclization of **2.115** driven by a phenolic hydroxyl group (R=H, Scheme 2.57). Use of the corresponding methyl ether resulted in a marked decrease in cyclization. The formation of palladium phenoxide **2.116** from a free hydroxyl group appeared to be pivotal for preorganization prior to macrocyclization.

Scheme 2.57



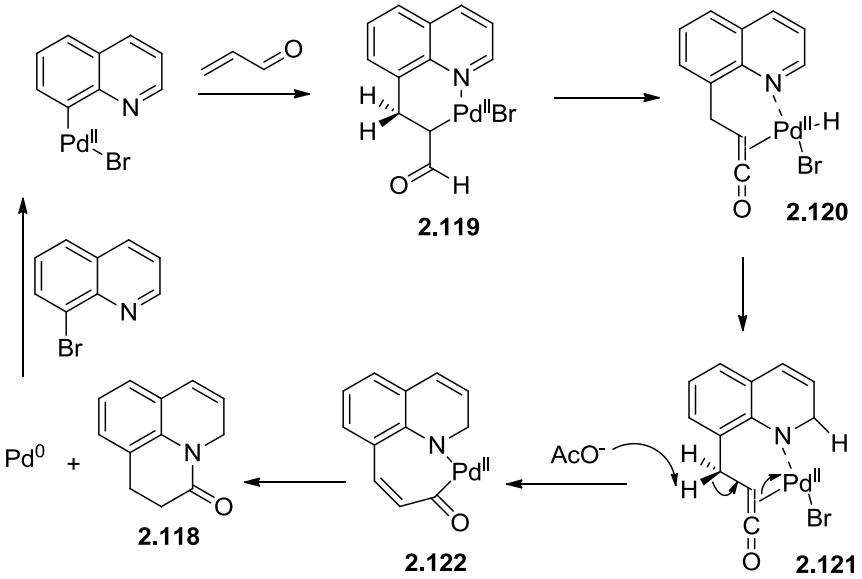
Another example of unusual behavior driven by chelation was observed by Pinel and coworkers.[122] The reaction of 8-bromoquinoline with acrolein diethyl acetal using the Herrmann-Beller catalyst[39] led to the formation of the saturated ester **2.117**, while the reaction with acrolein afforded a tricyclic quinolinone **2.118** (Scheme 2.58).

Scheme 2.58



To explain the outcome the authors proposed the following mechanism (Scheme 2.59). After the insertion step a six-membered palladacycle **2.119** is formed by coordination to the nitrogen. As a consequence, only the formyl hydrogen is conformationally accessible, thus forming a reactive ketene **2.120** upon β-hydride elimination. In the next step, a *syn* H-Pd addition to the C-N bond occurs followed by β-hydride elimination that leads to the formation of the intermediate **2.122** which undergoes reductive elimination to generate the tricyclic quinolinone **2.118**.

Scheme 2.59

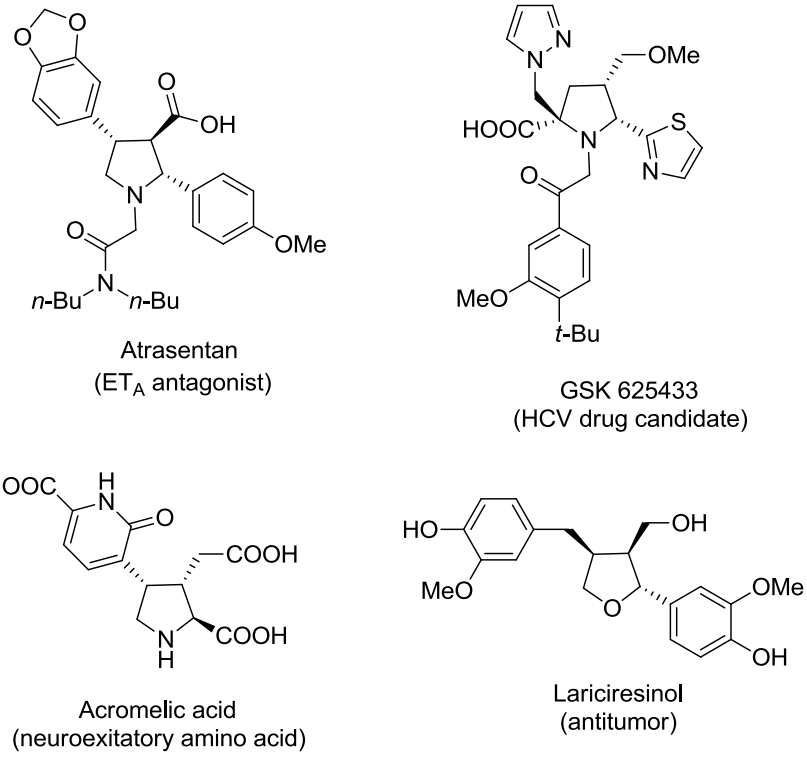

Pd^{II}
Br
O
N
H
H
Pd^{II}Br
O
H
2.119
Pd^{II}-H
Br
C
O
2.120
Br
Pd^0 +
O
2.118
Pd^{II}
O
2.122
AcO$^-$
H
H
Pd^{II}
Br
C
O
2.121

Chapter Three

Diastereocontrol in the Synthesis of 2,3,4-Trisubstituted Pyrrolidines and Tetrahydrofurans via a Palladium(II)-Catalyzed Three-Component Coupling Reaction.

A Variety of medicinally significant natural products and synthetic pharmaceutical agents contain substituted pyrrolidines and tetrahydrofurans as their structural cores.[123-124] Among these heterocycles, structures featuring an α-aryl functionality[125] as well as the neuroexcitatory amino acids[126] present particularly challenging targets for diastereocontrolled syntheses (Figure 1).

Figure 1

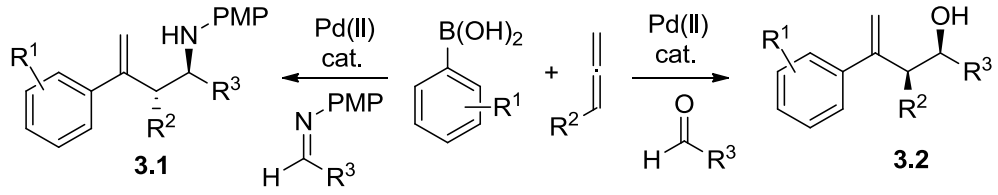


3.1 **Project Aim**:

As mentioned in introductory chapter, MCRs are excellent tools for diversity-oriented synthesis. Our group had reported a modular palladium-catalyzed three component syntheses of *N*-4-methoxyphenyl (*N*-PMP) protected homoallylic amines[127] and homoallylic alcohols.[128] The palladium-catalyzed three component

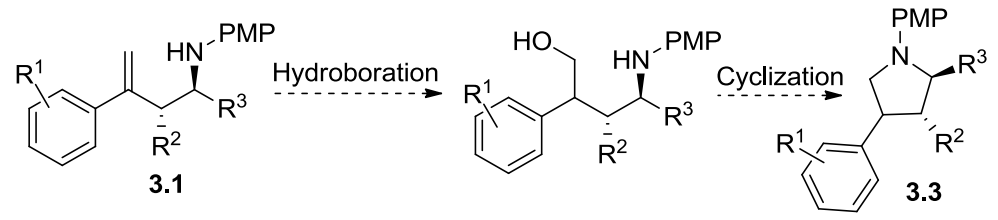
coupling of imines, allenes and boronic acids afforded diastereoenriched *N*-PMP protected homoallylic amines **3.1** with *anti*-stereochemistry. Replacing the imines with aldehydes, the reaction delivered diastereoenriched homoallylic alcohols **3.2** with *syn*-stereochemistry (Scheme 3.1).

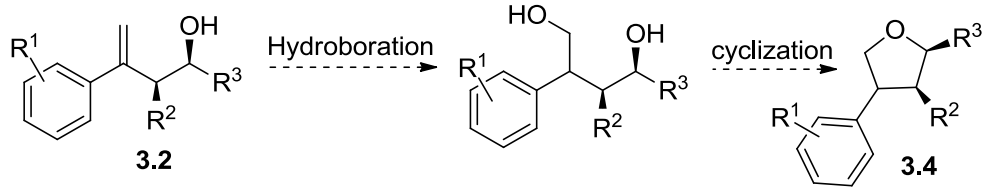
Scheme 3.1



The aim of this project was to demonstrate the utility of these homoallylic precursors to gain access to drug-like scaffolds as well as to unequivocally confirm the mechanistically significant stereochemical divergence in their preparation by completing a thorough structure assignment for the resulting pyrrolidines **3.3** and furans **3.4** (Scheme 3.2). We envisioned converting the *N*-PMP protected homoallylic amines to pyrrolidines and homoallylic alcohols to tetrahydrofurans using simple classical organic transformations. We proposed hydroboration followed by an intramolecular displacement of the primary alcohol would deliver the desired cyclized products.

Scheme 3.2

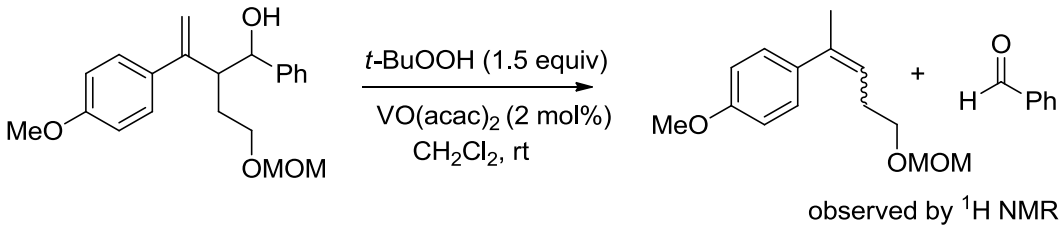




3.2 **Results and Discussion**:

As noted by Chad Hopkins, *N*-alkylation of *N*-PMP protected amines **3.1** required harsh conditions and at times did not produce desired results.[129] Moreover, the hydroboration of these amines was unsuccessful which is most likely due to interference caused by the basic amine functionality.[129] Also the PMP protecting group proved to be critical in the initial Pd-catalyzed three component coupling reaction. To overcome this problem, we planned to deprotect the *N*-PMP group and replace it with a non-interfering *N*-Ts protecting group. Thus my first challenge was to come up with a protocol for deprotection of the *N*-PMP group. Efforts to elaborate the homoallylic alcohols showed that in the presence of a base they underwent retroallylation to afford corresponding aldehyde and alkene (Scheme 3.3). So, I embarked on exploring feasibility of furan and pyrrolidine syntheses.

Scheme 3.3



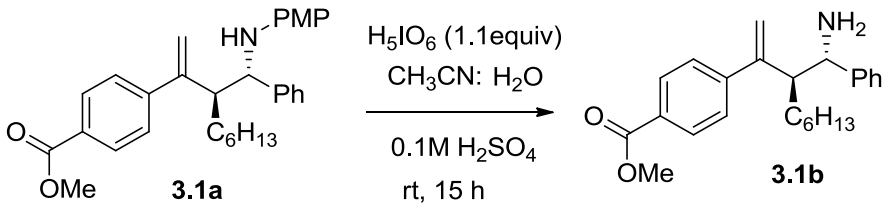
3.2.1 ***N*-PMP Deprotection and Tosylation**:

Most reports describe oxidative deprotection of *N*-PMP with ceric ammonium nitrate (CAN) at neutral pH.[130-133] But the disadvantage associated with this procedure is the requirement for excess of CAN (4-5 equiv), a laborious work-up and toxicity of CAN. Some of these drawbacks also apply to phenyl iodoacetate $PhI(OAc)_2$.[134-137] Based on these arguments I decided to use periodic acid (H_5IO_6)[138] as the oxidant, which is relatively less toxic, cheaper and easily accessible. Following is the description of *N*-PMP-deprotection.

To a yellow solution of the corresponding diastereomerically pure amine **3.1a** in MeCN was added solid H_5IO_6 (1.2 equiv) followed by H_2O (dropwise), and 1 M aq H_2SO_4. The resulting bright purple-red mixture was stirred at r.t. for 24 h. The mixture was diluted with H_2O, and extracted with Et_2O. For small-scale preparations, the crude mixture was directly loaded on the silica column for separation eluting with MeOH : CH_2Cl_2 mixture. Henceforth this protocol will be called as 'method A'.

Detailed workup optimization is described in Table 1. Upon completion of the reaction, TLC analysis showed a prominent base spot, the mixture was diluted with ether and quenched with saturated aq solution of $NaHCO_3$. The aqueous layer was extracted with ether. The combined ether layer was dried over Na_2SO_4, filtered and evaporated at r.t using rotavap. The crude mixture was purified using silica column chromatography. The pure amine was eluted in EtOAc : Hexane (5:1) mixture as yellow oil in 10% yield (entry 1). The low yield could be due adsorbtion of amines on to silica during column chromatography.

Table 1



Entry	H_5IO_6 (eq)	Work up	% yield
1	1.0	Normal[a]	10%
2	1.0	Normal and tried to isolate by prep TLC	0%
3	1.2	Work up at 0°C[b] and isolate by prep TLC	0%
4	1.2	Directly to flash column	55-75%

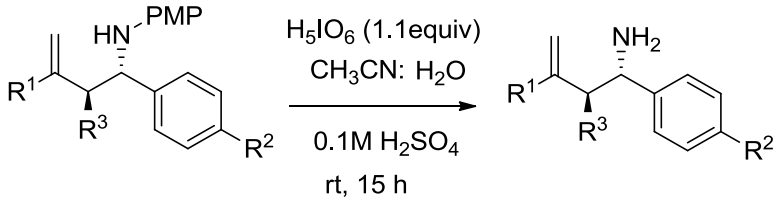
a) Normal workup: Neutralize the acidic reaction mixture with $NaHCO_3$ solution and extracted with Et_2O, dried over Na_2SO_4, and evaporated at RT using rotavap. b) used ice cold solutions

Substituting the chromatography with prep TLC after the workup or performing the workup at 0^oC did not improve the yield (entries 2 and 3). Interestingly, the desired amine was successfully isolated by not performing any aqueous workup, instead directly loading the reaction mixture onto the silica column and eluting with the MeOH : CH_2Cl_2 mixture to obtain reasonably pure amines in moderate yield (entry 4). (**Note**: Eluting with EtOAc : Hexane mixture gave lower yield).

Using the above optimized *N*-PMP deprotection protocol, Dr. Benoy, a postdoctoral associate in our lab successfully synthesized *N*-PMP deprotected amines **3.10**, **3.11** and **3.12** in good yields (Scheme 3.3). However, compound **3.9** afforded lower yields with method A. To overcome this problem, Benoy employed CAN mediated *N*-PMP deprotection to furnish compound **3.13** in moderate yield. The

procedure is as follows: To the solution of the diastereomerically pure amine **3.9** (1.0 equiv) in MeCN was added a solution of CAN (1.3 equiv) in H_2O at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 3h at r.t. EtOAc was added, and the mixture was washed with 5% aq $NaHCO_3$ and partially purified by silica column chromatography. Henceforth this protocol will be called 'method B'.

Scheme 3.3



3.6: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = CO_2Me; R^3 = *n*-hexyl — **3.10**: 73% (method A)

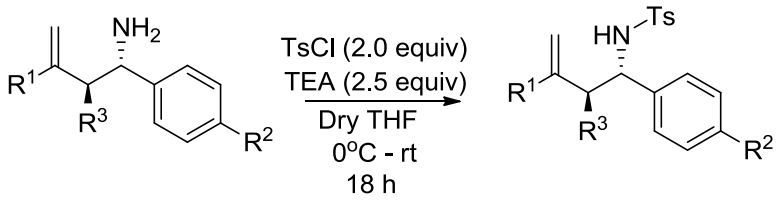
3.7: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = NO_2; R^3 = *n*-hexyl — **3.11**: 72% (method A)

3.8: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = CO_2Me; R^3 = 2-ethyl-1-hexyl — **3.12**: 76% (method A)

3.9: R^1 = 2-naphthyl; R^2 = CO_2Me; R^3 = *n*-hexyl — **3.13**: 48% (method B)

Deprotected amines **3.10**-**3.13** were obtained as brown to yellow oils that yielded acceptable ^1H and ^{13}C NMR spectra. However, they were not fully characterized and were quickly used for subsequent tosylation with tosyl chloride (TsCl). The primary amine (1.0 equiv) was dissolved in THF, TsCl (1.6 equiv) and Et_3N (1.1 equiv) were added to the solution at 0°C, and the mixture was stirred at r.t. under argon for 18 h. Quenched the reaction with H_2O and extracted with Et_2O. The organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford the crude product. Upon flash column chromatography using silica gel and eluting with EtOAc : Hexane mixture pure *N*-tosylamines **3.14**-**3.17** were isolated in good yields (62–72%) (Scheme 3.4).

Scheme 3.4



3.10: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = CO_2Me; R^3 = *n*-hexyl **3.14**: 64%

3.11: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = NO_2; R^3 = *n*-hexyl **3.15**: 62%

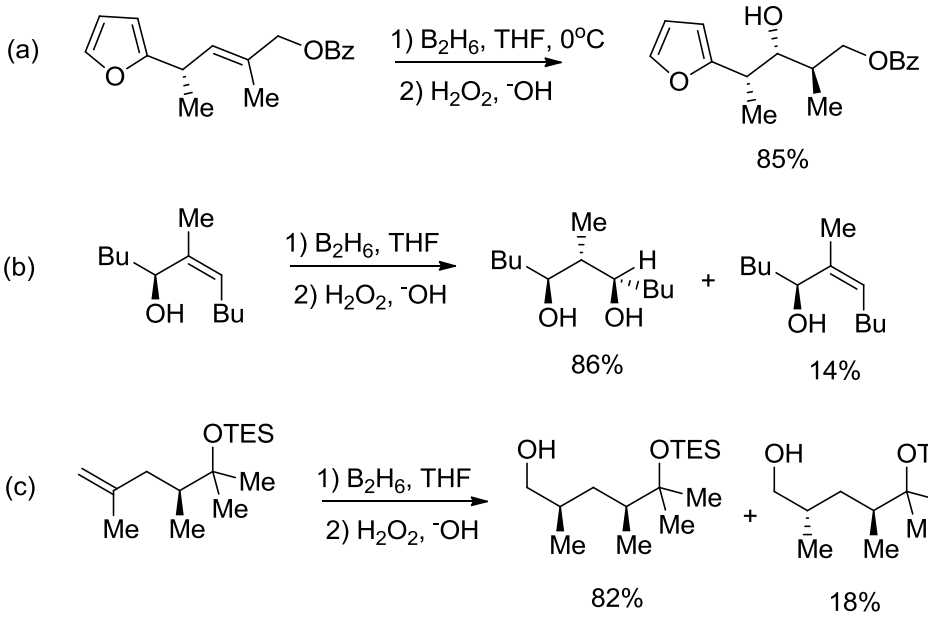
3.12: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = CO_2Me; R^3 = 2-ethyl-1-hexyl **3.16**: 72%

3.13: R^1 = 2-naphthyl; R^2 = CO_2Me; R^3 = *n*-hexyl **3.17**: 65%

3.2.2 **Hydroboration and Cyclization**:

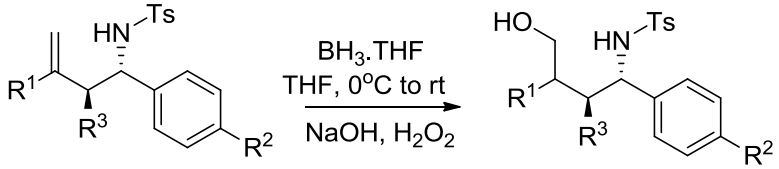
Protocols involving acyclic stereoinduction affording synthetically useful functionality are challenging. Asymmetric hydroborations of alkenes are outstanding examples of reactions which proceed with high acyclic stereoselection,[139-140] and have been employed in synthesis of many natural products.[141-143] Hydroboration with optically active boranes followed by oxidation gives optically active alcohols; often with high enantiomeric excess.[139-140] Chiral alkenes undergo attack by achiral boranes preferentially from one side of the double bond. This occurs when the chiral center is attached to the C which is attacked by the boron (Scheme 3.5a),[144] or when the chiral center is attached to the C to which hydride is transferred (Scheme 3.5b).[145] High asymmetric induction is found even when the chiral center is one atom away from the C to which hydride is being transferred (Scheme 3.5c).[146] Thus, chiral centers attached to either boron or to alkene C promote highly stereoselective reactions.

Scheme 3.5



Taking inspiration from these works Benoy successfully converted sulfonamides **3.14**-**3.17** to *N*-tosylamino alcohols using the standard conditions of BH_3.THF and H_2O_2 and NaOH. The protocol afforded *N*-tosylamino alcohols **3.18**-**3.21** in moderated to good yields as single diastereomers (Scheme 3.6) as confirmed by ^{1}H NMR. The Mechanistic rationale for diastereoselectivity is discussed later (section 3.4 *vide infra*).

Scheme 3.6



3.14: R^1 = *p*-(MeO_2C)C_6H_4; R^2 = CO_2Me; R^3 = *n*-hexyl **3.18**: 65%

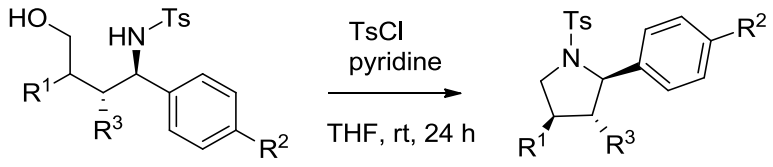
3.15: R^1 = *p*-(MeO_2C)C_6H_4; R^2 = NO_2; R^3 = *n*-hexyl **3.19**: 61%

3.16: R^1 = *p*-(MeO_2C)C_6H_4; R^2 = CO_2Me; R^3 = 2-ethyl-1-hexyl **3.20**: 66%

3.17: R^1 = 2-naphthyl; R^2 = CO_2Me; R^3 = *n*-hexyl **3.21**: 56%

The relative stereochemistry of the newly formed chiral center during hydroboration was not determined at this stage. The successful hydroboration on *N*-tosyl protected amines confirmed the interference of *N*-PMP protected amines as noted by Hopkins. Thus replacing the *N*-PMP group with *N*-tosyl was crucial for the success of hydroboration. Other hydroborating reagents[147] surveyed ($BH_3 \cdot SMe_2$ and 9-BBN-H) led only to low conversions of substrates. Finally, treating with TsCl and pyridine,[148] Benoy was able to convert *N*-tosylamino alcohols **3.18**-**3.21** into desired pyrrolidines **3.22**-**3.25** as single diastereomers in good to high yields (66–86%) (Scheme 3.7).

Scheme 3.7



3.18: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = CO_2Me; R^3 = *n*-hexyl **3.22**: 66%

3.19: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = NO_2; R^3 = *n*-hexyl **3.23**: 82%

3.20: R^1 = *p*-$(MeO_2C)C_6H_4$; R^2 = CO_2Me; R^3 = 2-ethyl-1-hexyl **3.24**: 78%

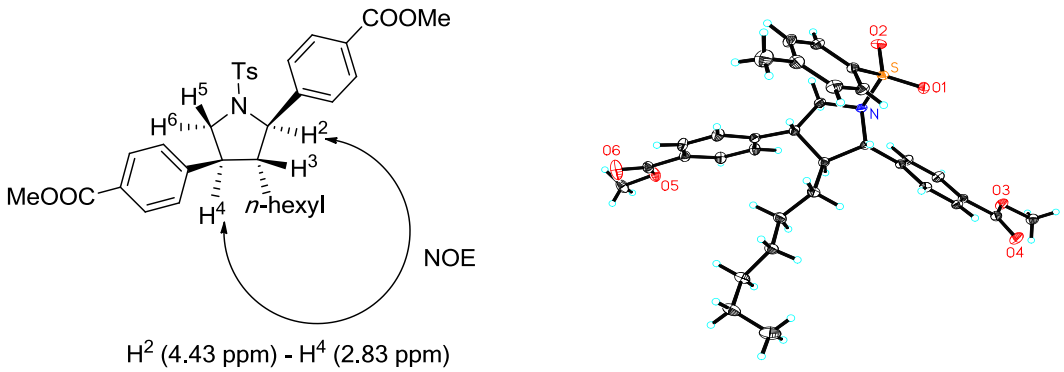
3.21: R^1 = 2-naphthyl; R^2 = CO_2Me; R^3 = *n*-hexyl; **3.25**: 86%

The relative stereochemistry was assignment based on the X-ray crystallographic analysis of a single crystal of pyrrolidine **3.22** which unequivocally established its relative stereochemistry as 2,3-*anti* and 3,4-*anti*, confirming the original assignment of homoallylic amines as *anti* (Scheme 3.1).[127] This also confirmed the stereochemical course of the hydroboration reaction. I calibrated the nuclear Overhauser effect (NOE) analysis using the compound **3.22**. This was used to

establish the relative stereochemistry of amino acid derivative which is discussed later in the following section. Selective nuclear Overhauser effect (NOE) analysis of pyrrolidine **3.22** revealed the indicative correlation between the *syn*-hydrogens at C-2 and C-4 (Figure 2). The relative stereochemistry of pyrrolidines **3.23**-**3.25**, were assigned by analogy with product **3.22**.

Thus utilizing my optimized *N*-PMP deprotection and *N*-tosylation protocols, Dr. Benoy successfully converted structurally flexible *N*-PMP protected amines **3.6**-**3.9** to rigid pyrrolidines **3.22**-**3.25**. Using the X-ray analysis of the pyrrolidines**3.22**, he was able to unequivocally confirm the relative stereochemistry of the homoallylic amines (*anti*) as previously reported from our group.[127]

Figure 2

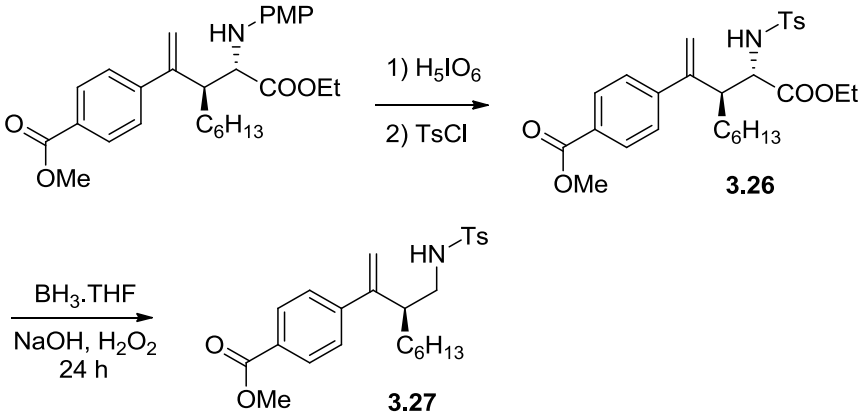


3.2.3 **Amino acid derivative**:

We were interested to apply the above ring closing sequence to the preparation of pyrrolidines with α-amino ester functionality; an important motif seen in the neuroexcitatory amino acids (see Figure 1). During this study, an interesting observation was made by Dr. Benoy. He had observed an unexpected decarboxylation

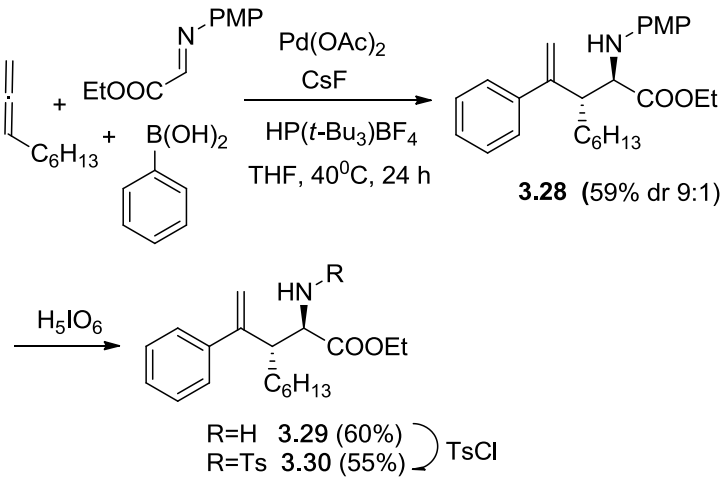
(loss of ester motif) of compound **3.26** during hydroboration and afforded amine **3.27** (Scheme 3.8). The decarboxylation could be potentially due to stronger basic oxidative conditions used in hydroboration reaction. Unfortunately, at this point Benoy had to leave our group and I was assigned the task of solving the decarboxylation problem.

Scheme 3.8



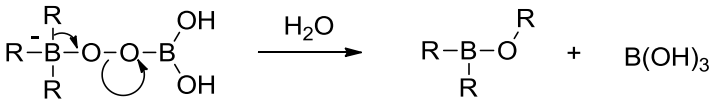
The *N*-PMP-protected amine **3.28** was synthesized (dr 9:1) in 59% yield after column chromatography (Scheme 3.9). The derivative was selected with the goal to have a single ester motif in the molecule unlike compound **3.26** which has two ester groups. The established PMP removal/tosylation sequence afforded *N*-tosylamine **3.30** as a single diastereomer in acceptable yields (60% deprotection, 55% tosylation). The synthesis required no purification of the intermediate deprotected amine **3.29**.

Scheme 3.9



I envisioned the use of milder oxidizing agent instead of H_2O_2 would be the right initial step in overcoming the decarboxylation problem. Kabalka[149] notes that use of H_2O_2 sometimes requires quite harsh conditions that are incompatible with many functional groups for the oxidation of organoboranes, while sodium perborate offers an interesting mild alternative. He assumes that the mild nature of the oxidant is a result of having borate as a leaving group as compared to hydroxide, which is formed in hydrogen peroxide oxidations (Scheme 3.10)

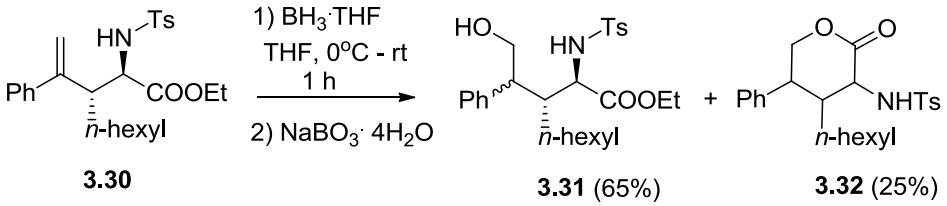
Scheme 3.10



It was exciting to observe that compound **3.30** under milder basic conditions ($NaBO_3$)[149] and with a limited reaction time for the oxidation (1 h max) delivered the desired *N*-tosylamino alcohol **3.31** as a single diastereomer in good yield (65%)

(Scheme 3.11). Unexpectedly, lactone **3.32** formed via an intramolecular lactonization was also isolated in 25% yield. Again no attempt was made to elucidate the relative stereochemistry of the newly formed stereocenter.

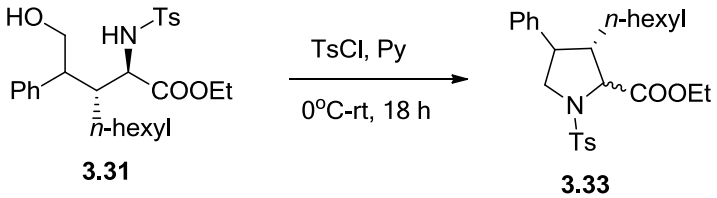
Scheme 3.11



3.30 **3.31** (65%) **3.32** (25%)

Treatment of *N*-tosylamino alcohol **3.31** with TsCl and pyridine[148] provided a mixture of diastereomeric pyrrolidines as observed in ^{1}H-NMR (Scheme 3.12). The formation of a diastereomeric mixture could be due to the epimerization of the sensitive α-amino ester functionality. However the ring closure was successfully performed under milder Mitsunobu conditions[150] which afforded the desired pyrrolidine **3.33** as a single diastereomer in an excellent yield (84%) (Scheme 3.13).

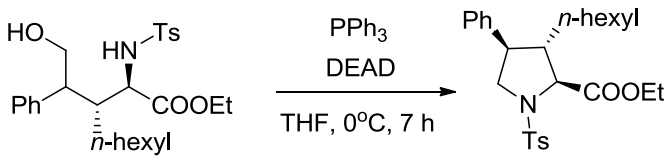
Scheme 3.12



3.31 **3.33**

observed epimerization (^{1}H NMR)

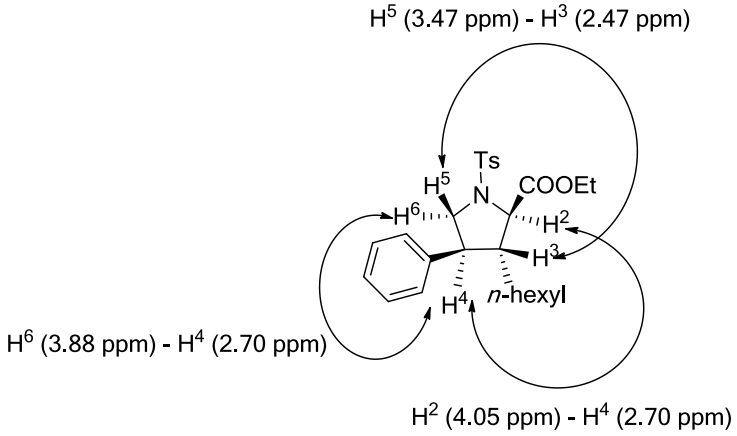
Scheme 3.13



3.31 **3.33** (84%)

The relative stereochemistry for pyrrolidines **3.33** was assigned based on the calibrated NOE correlation (pyrrolidine **3.22**, Figure 2) which indicated the *anti*, *anti* relative stereochemistry. The correlation was seen for the *syn*-hydrogens at C-2 and C-4, as well as that of hydrogens H-3 and H-5 shown in (Figure 3).

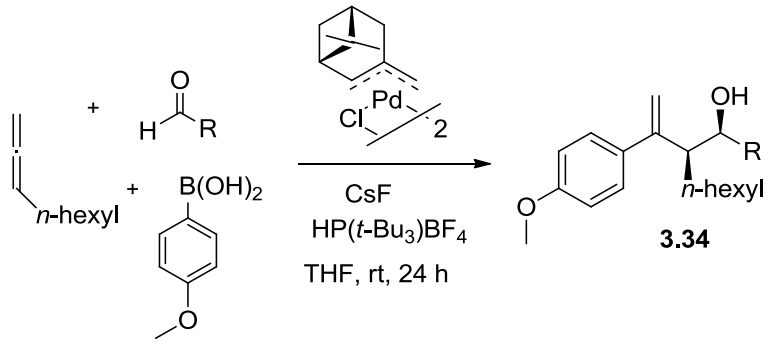
Figure 3



3.2.4 **2,3,4-Trisubstituted Tetrahydrofurans**:

We recognized that the successful application of the above hydroboration and ring closing protocol to homoallylic alcohols **3.34** would open up access to trisubstituted tetrahydrofurans structurally related to biologically active lignans[151] (Figure 1). Alcohols **3.34a**–**d** were prepared by the palladium-catalyzed MCR reported by our group.[128] As reported, mixtures of diastereomeric alcohols (determined by ^{1}H NMR spectroscopy) were produced, and the single major diastereomers **3.34a**–**d** were easily isolated from the crude reaction mixtures, using column chromatography, in 54–65% yield (Scheme 3.14).

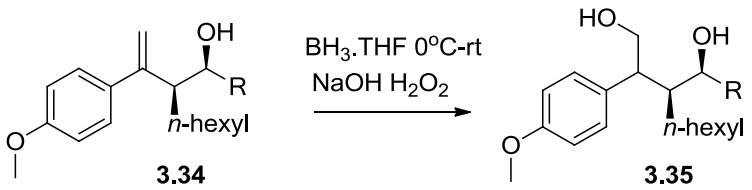
Scheme 3.14



R = C_6H_5	**3.34a**: 65%
R = *p*-(MeO)C_6H_4	**3.34b**: 54%
R = *p*-(NO_2)C_6H_4	**3.34c**: 55%
R =2-furyl	**3.34d**: 60%

Applying the previously established hydroboration conditions to homoallylic alcohols **3.34** afforded diols **3.35a-d**. Disappointingly, unlike the hydroboration of homoallylic amines the diastereoselectivity of the hydroboration of the alcohols suffered, and diols **3.35a-d** were isolated as 3:1 mixtures of chromatographically inseparable diastereomers (Scheme 3.15) (determined by ^{1}H NMR spectroscopy). The relative stereochemistry of major and minor diols was not assigned at this stage. A Mechanistic rationale for the diastereoselectivity is discussed later in the following section.

Scheme 3.15



3.34a: R = C_6H_5 **3.35a**: 85% , dr 3:1

3.34b: R = *p*-(MeO)C_6H_4 **3.35b**: 92% , dr 3:1

3.34c: R = *p*-(NO_2)C_6H_4 **3.35c**: 62% , dr 3:1

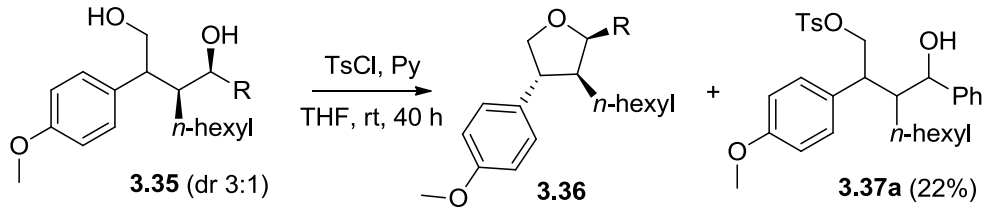
3.34d: R =2-furyl **3.35d**: 68%, dr 3:1

Diols **3.35b** and **3.35d** showed few additional signals in ^{13}C NMR. This is potentially due to dehydration caused by acid contaminated $CDCl_3$. The additional signals disappeared when the sample filtered through plug of basic alumina was used (spectra enclosed).

We were pleased to note that the treatment of the 3:1 diastereomeric mixture of diols **3.35a**–**d** with TsCl and pyridine afforded tetrahydrofurans **3.36a**–**d** as single diastereomers (as analyzed from ^1H NMR) and a monotosylated alcohol **3.37a** (22%) (Scheme 3.16). Although the yields of tetrahydrofurans **3.36a**–**d** were only moderate to good (60-73%), the isolation of single diastereomers proved to be a synthetically practical process. The relative stereochemistry of compound **3.37a** was not established. The corresponding monotosylated alcohol compounds **3.37b-d** were not isolated but were observed in crude ^1H NMR. The mass balance ratio of **3.36**:**3.37** approximately 3:1, is similar to the diastereomeric ratio of diols. Therefore we believe that the tetrahydrofurans are derived from the respective major diastereomers of diols

and the monotosylated alcohols are produced from the minor diastereomers of the diols.

Scheme 3.16



3.35a: R = C_6H_5 **3.36a**: 65%, dr 1:0[a]

3.35b: R = *p*-(MeO)C_6H_4 **3.36b**: 73%, dr 1:0[a]

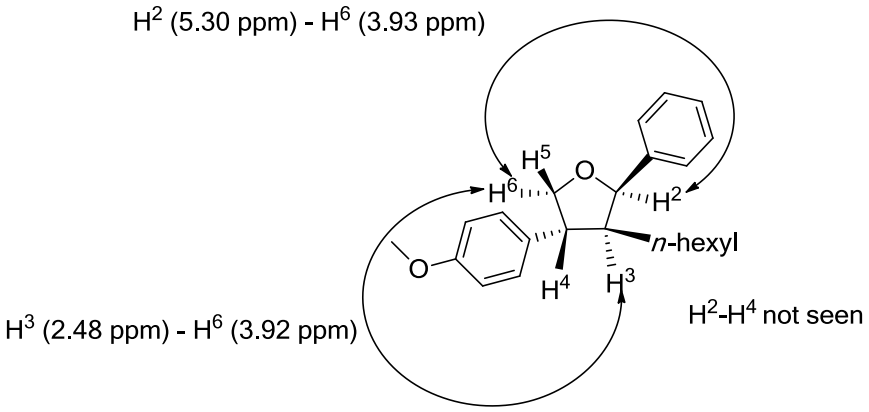
3.35c: R = *p*-(NO_2)C_6H_4 **3.36c**: 65% , dr 1:0[a]

3.35d: R =2-furyl **3.36d**: 60%, dr 1:0[a]

[a)] dr ratio based on ^{1}H NMR

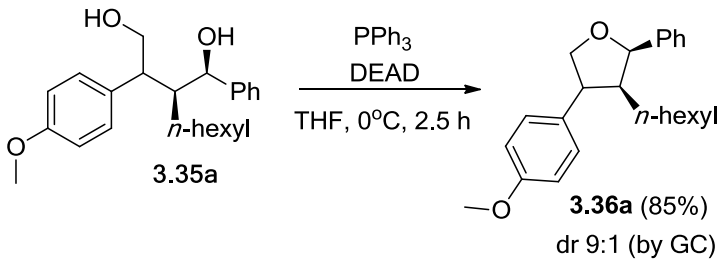
The relative stereochemistry of tetrahydrofuran **3.36a** was assigned based on selective NOE analysis. The indicative signals in the NOE spectra showed the correlation of hydrogens H-2/H-3 with the same hydrogen H-6 and absence of H-2 and H-4 correlation. Thus it was concluded that tetrahydrofuran **3.36a** possessed *syn*, *anti* relative stereochemistry (Figure 4). The structures of analogous furans **3.36b**–**d** were assigned based on the NOE correlations. The above results are in agreement with the previously assigned *syn*-stereochemistry for the major diastereomers of homoallylic alcohols **3.34**.[128]

Figure 4



The ratio of **3.36**:**3.37** is approximately 3:1 which is similar to the diastereomeric ratio of diols **3.35**. Based on this data we believe that the major diastereomer of the diol undergoes ring closure faster than the minor diastereomer under these conditions. To answer the question if the minor diastereomer of the diol undergoes cyclization, the diastereomeric mixture of diol **3.35a** was treated with Mitsunobu conditions. Surprisingly, unlike the TsCl/Py conditions which afforded mixture of tetrahydrofurans and monotosylated alcohol (Scheme 3.15), the Mitsunobu reaction afforded tetrahydrofuran **3.36a** in high yield (85%) as a mixture of chromatographically inseparable diastereomers (dr 9:1 by GC analysis). (Scheme 3.17). So the minor diastereomer did cyclize under Mitsunobu conditions.

Scheme 3.17



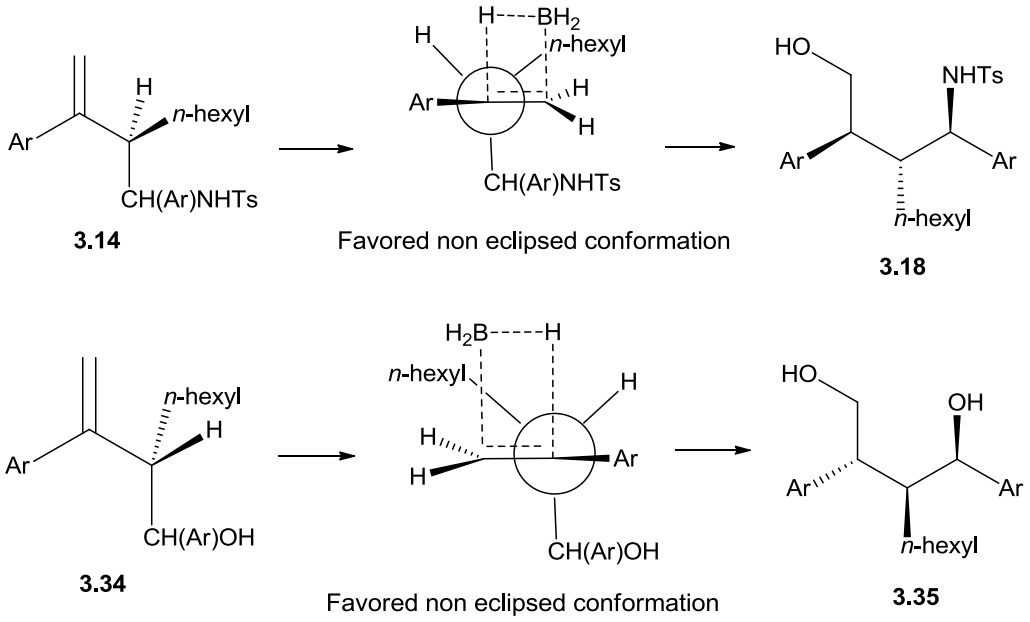
3.3 **Mechanistic Rationale for Stereochemical Outcome in Hydroboration Reaction**:

The transformation of a prochiral group into a chiral center can be achieved by (a) the use of a chiral reagent (reagent control of stereoselectivity)[61, 152] or (b) as a consequence of asymmetric induction by stereocenters already present in the substrate (substrate control of diastereoselectivity).[153-154] The facial selectivity of the hydroboration of homoallylic amines and alcohols appears to arise from a substrate-directed approach of borane (BH_3) to the olefin.[145] The notion that non-eclipsed conformation of the transition states operates in such hydroboration reactions is strongly supported.[155-156] Using this model of non-eclipsed transition state, Evans explained the stereochemical outcome of hydroboration in the synthesis of Lonomycin A.[157]

The stereochemical outcome of our hydroboration reaction can be explained using the concept of substrate controlled approach and the non-eclipsed transition state. The diastereomers of the non-eclipsed transition states in which the steric interactions between the *n*-hexyl and C-3 aryl groups in the substrates are minimized

are shown in Figure 5.[157] The approach of BH_3 from the face opposite to the 'large' substituent at the allylic carbon delivers the observed alcohols. The more efficient diastereocontrol observed in the hydroborations of *N*-tosyl amines **3.14-3.17** and **3.30** correlates with the greater steric bulk of the *N*-tosyl group in comparison with the hydroxy group in alcohols **3.34a-d**.

Figure 5



3.4 **Conclusions**:

Using a Pd-catalyzed MCR followed by two or three classical transformations the easily accessible building blocks were converted to medicinally relevant drug like molecules. Boronic acids, allenes, and imines or aldehydes were converted into single diastereomers of contiguously trisubstituted 2,3-*trans* and 3,4-*trans*-pyrrolidines or 2,3-*cis* and 3,4-*trans*–tetrahydrofurans, respectively.[158] The

homoallylic amines and alcohols, which served as precursors for pyrrolidines and tetrahydrofurans respectively, were rapidly assembled via Pd-catalyzed MCR, thus showcasing the importance of MCRs. The MCR sets up the stereocenters at C2 and C3 positions of cyclized products. A substrate controlled hydroboration establishes the C4 stereocenter.

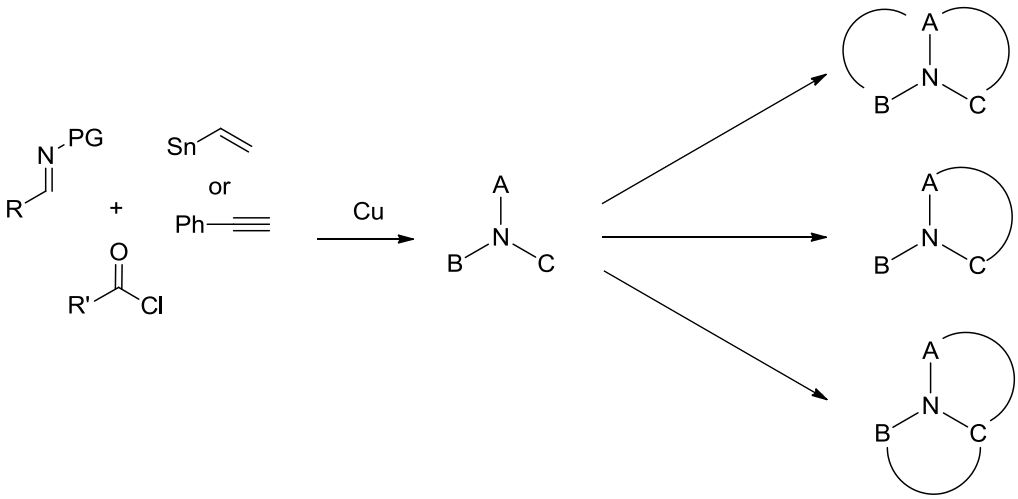
Unequivocal assignment of the relative stereochemistry in the heterocycles was achieved and serves to confirm the stereochemical divergence observed in the previously reported palladium-catalyzed three component preparation of homoallylic alcohols (*syn*) and homoallylic amines (*anti*). The modular synthetic sequence can be applied towards the construction of combinatorial libraries of pyrrolidines with structures related to biologically active natural products and synthetic pharmaceutical agents. Also, the methodology reported herein opens up possible future application towards synthesis of potent ET_A antagonist-atrasentan and natural products like kainic acid and acromelic acid.

Chapter Four

Divergent Reaction Pathways of Homologous and Isosteric Propargyl Amides in Sequential Ru/Pd-Catalyzed Annulations for the Synthesis of N-Heterocycles.

The Malinakova lab is actively involved in developing methodologies amenable for diversity oriented and combinatorial library synthesis.[44-45] One of the efficient strategies we employ is sequencing Cu-catalyzed MCR with transition metal-catalyzed annulation reactions giving rapid access to diverse heterocycles (Figure 1).[159] In this chapter, the methodology development and interesting mechanistic insights observed during RCEYM and Heck annulations will be discussed in detail. The built-in potential of the methodology to incorporate diversity points in MCR followed by varied annulations is the key for the design and synthesis of combinatorial library with multiple distinct core structures. Therefore, along with studying fundamental interesting chemistry, the methodology has its utility in diversity oriented synthesis of drug like heterocycles.

Figure 1



4.1 **Results and Discussions**:

My first project involved sequencing a MCR generating enyne precursors, with Ru/Pd catalyzed cyclization reactions.

4.1.1 **Synthesis of Enyne Precursors**:

Looking for the MCR protocol to assemble the enyne precursors we found that the methodology reported by Arndtsen[160] was well suited for our goals. This protocol would allow us to access functionalized 1,6-enynes and 1,7-enynes. Arndtsen described an elegant Cu-catalyzed MCR of imines, acid chlorides and terminal alkynes to synthesize propargylamides **4.1** (Scheme 4.1) in good to excellent yields (Table 1)

Scheme 4.1

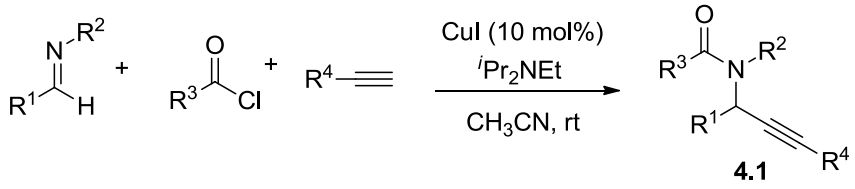
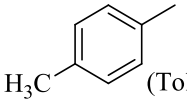
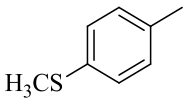
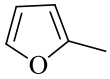
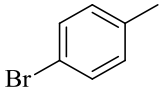
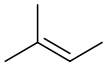
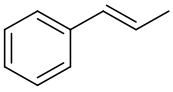
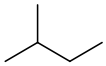


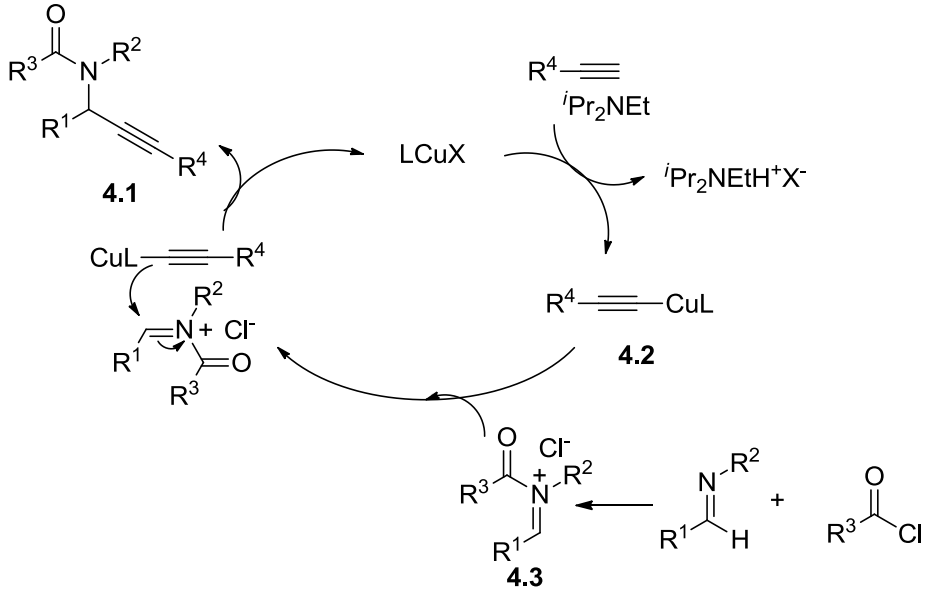
Table 1

Entry	R^1	R^2	R^3	R^4	4.1 (%)
1		Bn	Ph	Ph	95
2		Et	Ph	Ph	87
3		Bn	Ph	TMS	77
4		Et		Ph	81
5		Bn		Ph	93

6	Tol	Ph	Ph	Ph	99
7	Tol	Et	Ph	CH_2Cl	84
8	Tol	Bn	Ph	CH_2OAc	89

The ^{1}H-NMR monitoring of the reaction revealed that CuI is immediately converted to the copper acetylide **4.2**, and the imine quickly reacts with acid chloride to form *N*-acyliminium salt **4.3**. Moreover, the control experiments demonstrated that the addition of imine and acid chloride to CuI does not lead to any appreciable oxidative addition in contrast to the palladium-catalyzed cross-coupling reactions. Based on this information the following mechanism was proposed (Scheme 4.2). A nucleophilic attack of copper acetylide **4.2** on *insitu* generated *N*-acyl iminium ion **4.3** delivers the desired propargylamide **4.1**.

Scheme 4.2

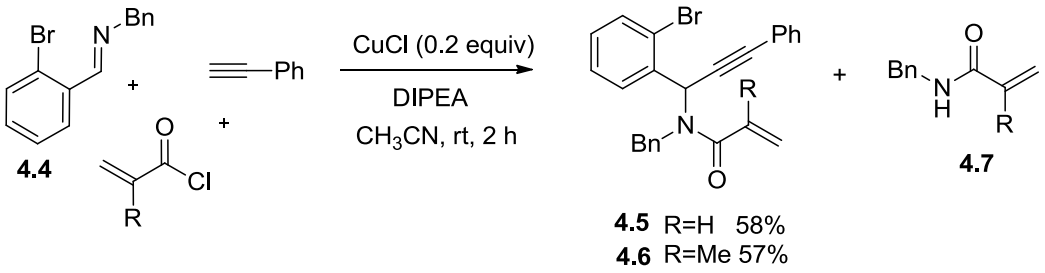


Method Development:

We decided to use R^1= *o*-bromo substituted aryl/heteroaryl ring and R^2 = *N*-allyl or homoallyl (Scheme 4.1) which were not reported by Arndtsen (Table 1). This would provide us with the required functional handle for subsequent RCEYM and Heck annulation. Using the Arndtsen protocol, we began exploring the synthesis of required enynes. The initial line of thought was to use acryloyl chloride as the source of acyl chloride wherein, the C=C motif of the acryloyl chloride would serve as the 'ene' component for the subsequent RCEYM (Scheme 4.3). Note the incorporation of *o*-bromo motif in the imine substrate **4.4**.

All imines were prepared according to a modified literature procedure[161] by condensation of a 1 : 1 mixture of aldehyde and amine in methylene chloride in the presence of activated 3Å (8-12 mesh) molecular sieves for 24 h at rt followed by filtration through celite and removal of solvent under vacuum to afford pure imines that were used immediately.

Scheme 4.3



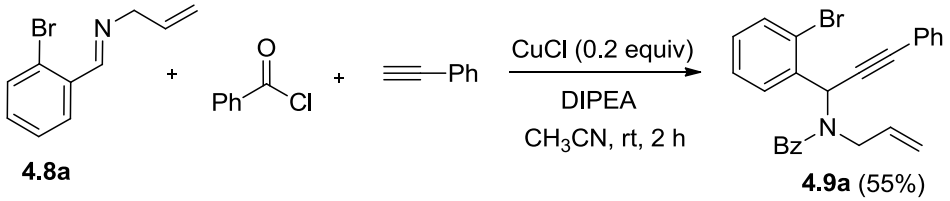
The yields of the enynes **4.5** and **4.6** were moderate due to the formation of corresponding amide side product **4.7**. This is formed because the acyl iminium ion

intermediate is very sensitive to the moisture and undergoes hydrolysis. Therefore it was important to perform the reaction under strictly anhydrous conditions. During purification it was observed that DIPEA co-eluted with the product when silica was used for column chromatography. Efficient separation and purification was achieved with basic a alumina column.

Following is the experimental procedure of how the enynes were synthesized. Henceforth this procedure will be addressed as "conditions A". The mixture of imine and excess of benzoyl chloride and alkyne (1.5 equiv) in acetonitrile (5-10 mL) was premixed in a 25mL 2-neck round bottom flask and stirred for 5 min at rt under argon. This generates the *N*-acyliminium ion. The resulting yellow solution and neat *i*Pr_2NEt (1.5 equiv) were added dropwise simultaneously to a solution of CuCl (0.2 equiv) in acetonitrile (2 mL) resulting in formation of yellow precipitate. The reaction mixture was stirred at rt under argon for 2 h. Solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over basic alumina eluting with EtOAc/Hexanes mixtures to yield pure enynes.

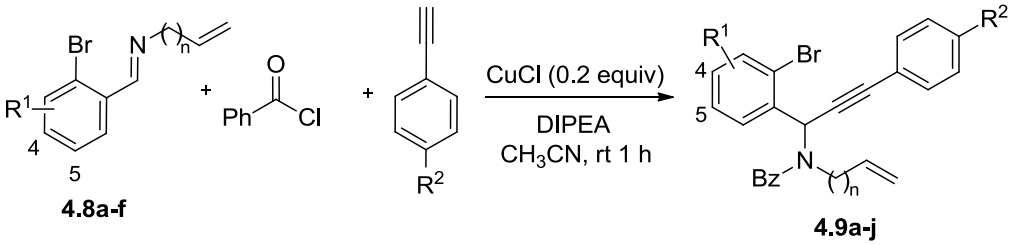
Enynes **4.5** and **4.6** proved to be challenging substrates for RCM (Scheme 4.8 *vide infra*). Enyne **4.5** produced an approximately (3:2) mixture of cyclic constitutional isomers. This poor selectivity in RCEYM forced us to transpose the amide carbonyl away from the ene component. Thus, using the imine generated from allyl amine **4.8a** in the aforementioned Cu-catalyzed MCR, the desired 1,6-enyne **4.9a** was synthesized in moderate yield (Scheme 4.4).

Scheme 4.4



Pleased with this result series of 1,6 and 1,7-enynes were synthesized using conditions A (Table 2).

Table 2

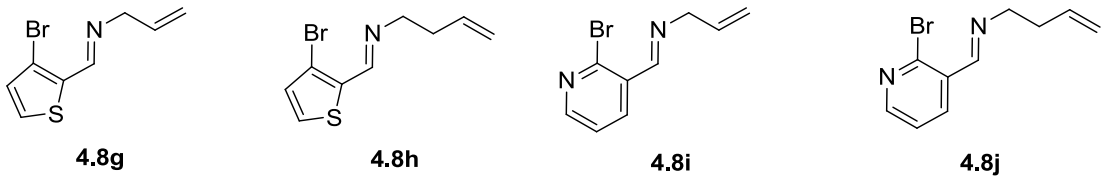


Entry	Imines (4.8)	n	R^1	R^2	Enynes (4.9)	% yield
1	**4.8a**	1	H	H	**4.9a**	55
2	**4.8b**	1	4,5-$(OMe)_2$	H	**4.9b**	49
3	**4.8c**	1	5-F	H	**4.9c**	52
4	**4.8a**	1	H	F	**4.9d**	53
5	**4.8a**	1	H	OMe	**4.9e**	61
6	**4.8d**	2	H	H	**4.9f**	55
7	**4.8e**	2	4,5-$(OMe)_2$	H	**4.9g**	45
8	**4.8f**	2	5-F	H	**4.9h**	52
9	**4.8d**	2	H	F	**4.9i**	58

10	**4.8d**	2	H	OMe	**4.9j**	53

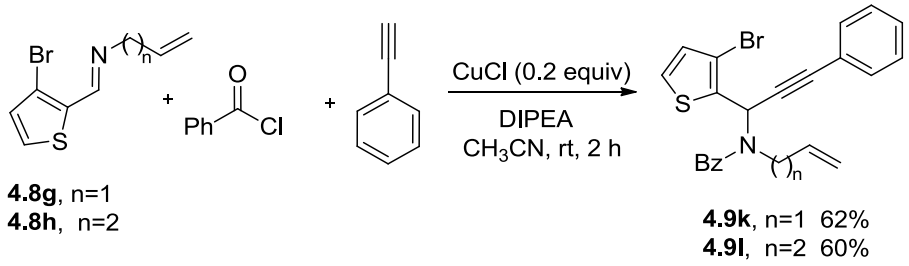
Aiming to diversify and incorporate additional heteroatoms, the following heteroaromatic imines **4.8g-j** were synthesized (Figure 2) and used in Cu-catalyzed MCR.

Figure 2

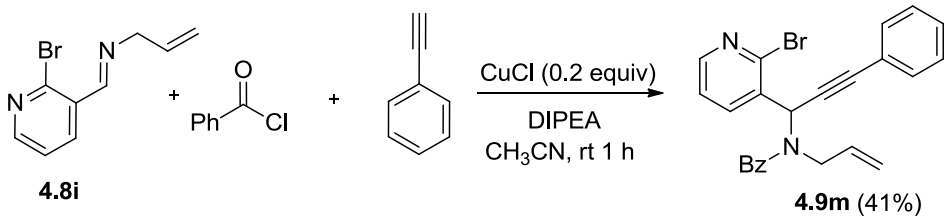


Thiophene derived imines **4.8g-h** delivered enynes **4.9k-l** in similar yields as that of non-heteroaromatic imines, under conditions A (Scheme 4.5). On the contrary, pyridine derived imine **4.8i** afforded lower yield (41%) of enyne **4.9m** (Scheme 4.6). This could be due to the electron withdrawing nature of the pyridine ring which increases the electrophilicity of *N*-acyliminium ion and makes it more susceptible to hydrolysis.

Scheme 4.5



Scheme 4.6



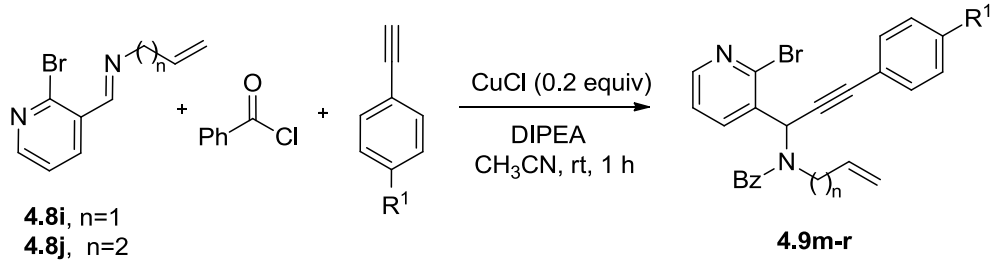
4.8i

4.9m (41%)

To address the problem of low yield in the pyridine case **4.8i**, I reversed the order of addition of *N*-acyliminium and CuCl solutions. In conditions A the solution of *N*-acyliminium was drawn out and injected along with neat DIPEA into the solution of CuCl in acetonitrile. This exposed iminium ion to air during withdrawing and injecting process. In modified conditions the CuCl solution and neat DIPEA was added to the solution of iminium ion, thus minimizing the exposure of iminium ion to air and thereby reducing the hydrolysis to some extent. The modified conditions will be called "conditions B" and are as follows: The solution of imine (1.0 equiv) and excess of benzoyl chloride and phenylacetylene (1.2 equiv) in acetonitrile (5 mL) was stirred at rt under argon for 5 min. to afford a yellow solution of *N*-acyliminium ion. Note the use of lower equivalent of benzoyl chloride as compared to conditions A. This was to avoid formation of *N*-benzoyl pyridinium ion. To this solution neat DIPEA (1.2 equiv) and the solution of CuCl (0.2 equiv) in acetonitrile (1 mL) were added simultaneously dropwise. The reaction mixture was allowed to stir at rt under argon for 1 h. Solvents were removed under reduced pressure and the resulting crude product was separated by flash chromatography over silica eluting with

EtOAc/Hexanes mixtures to yield pure enyne **4.9m** (Table 3). Pleased with this result two more analogs of 1,6-enynes and three analogs of 1,7-enynes were synthesized.

Table 3



4.8i, n=1
4.8j, n=2

4.9m-r

Entry	Imines (4.8)	n	R^1	Enynes (4.9)	% yield
1	**4.8i**	1	H	**4.9m**	59
2	**4.8i**	1	F	**4.9n**	60
3	**4.8i**	1	OMe	**4.9o**	62
4	**4.8j**	2	H	**4.9p**	62
5	**4.8j**	2	F	**4.9q**	61
6	**4.8j**	2	OMe	**4.9r**	63

The signals in ^{1}H-NMR spectrum of all these enynes were broad and short (Figures 3 and 4). This is due to existence of rotamers caused by the restricted rotation along the amide bond. One of the analogs from the 1,6-enyne series (Figure 3) and 1,7-enynes series (Figure 4) were picked to perform the ^{1}H-NMR spectroscopy at higher temperature. As the temperature increased, the signals sharpened and also gave the expected integration.

Figure 3

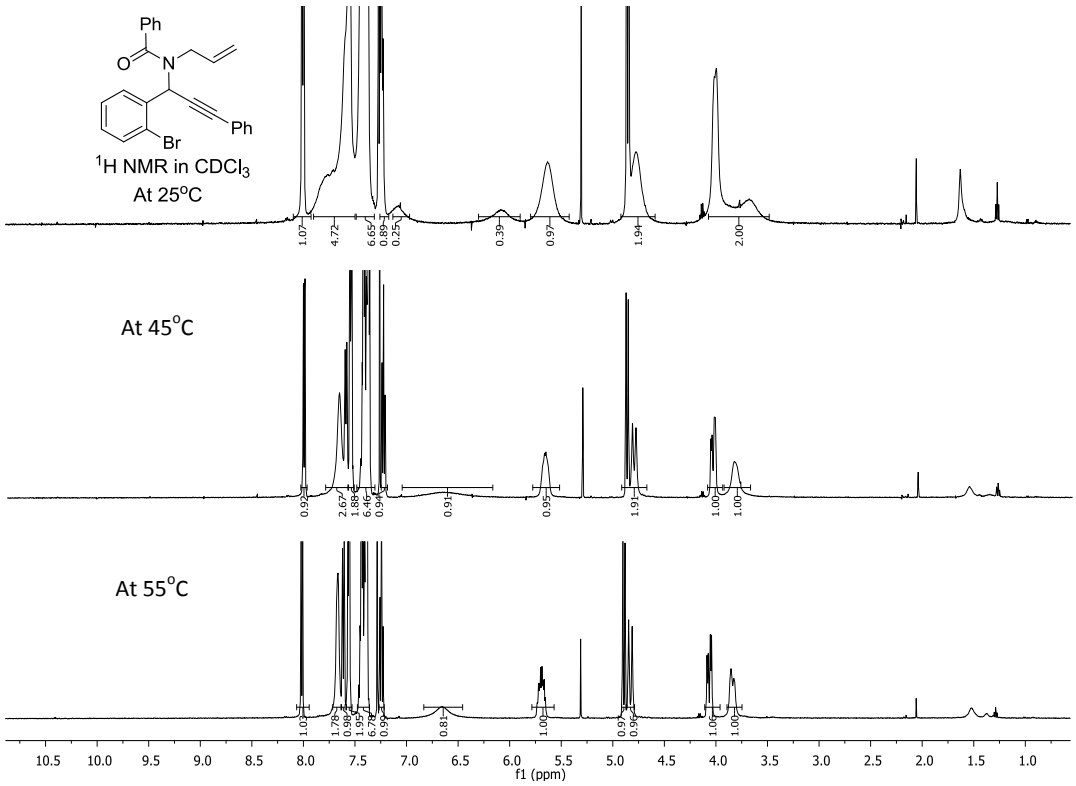
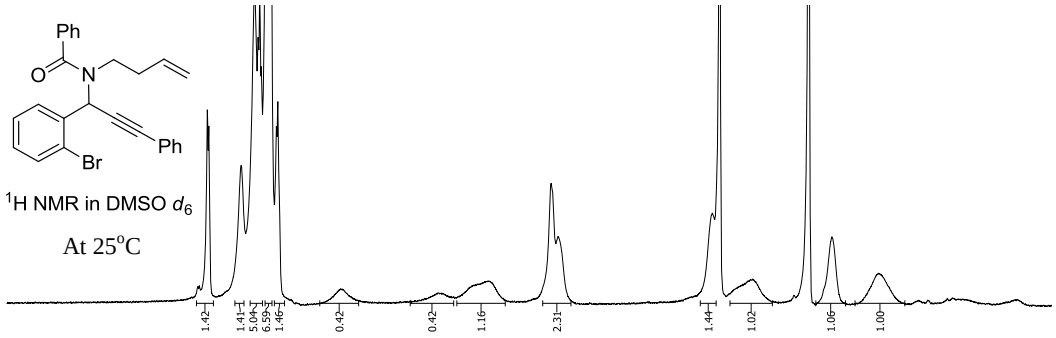
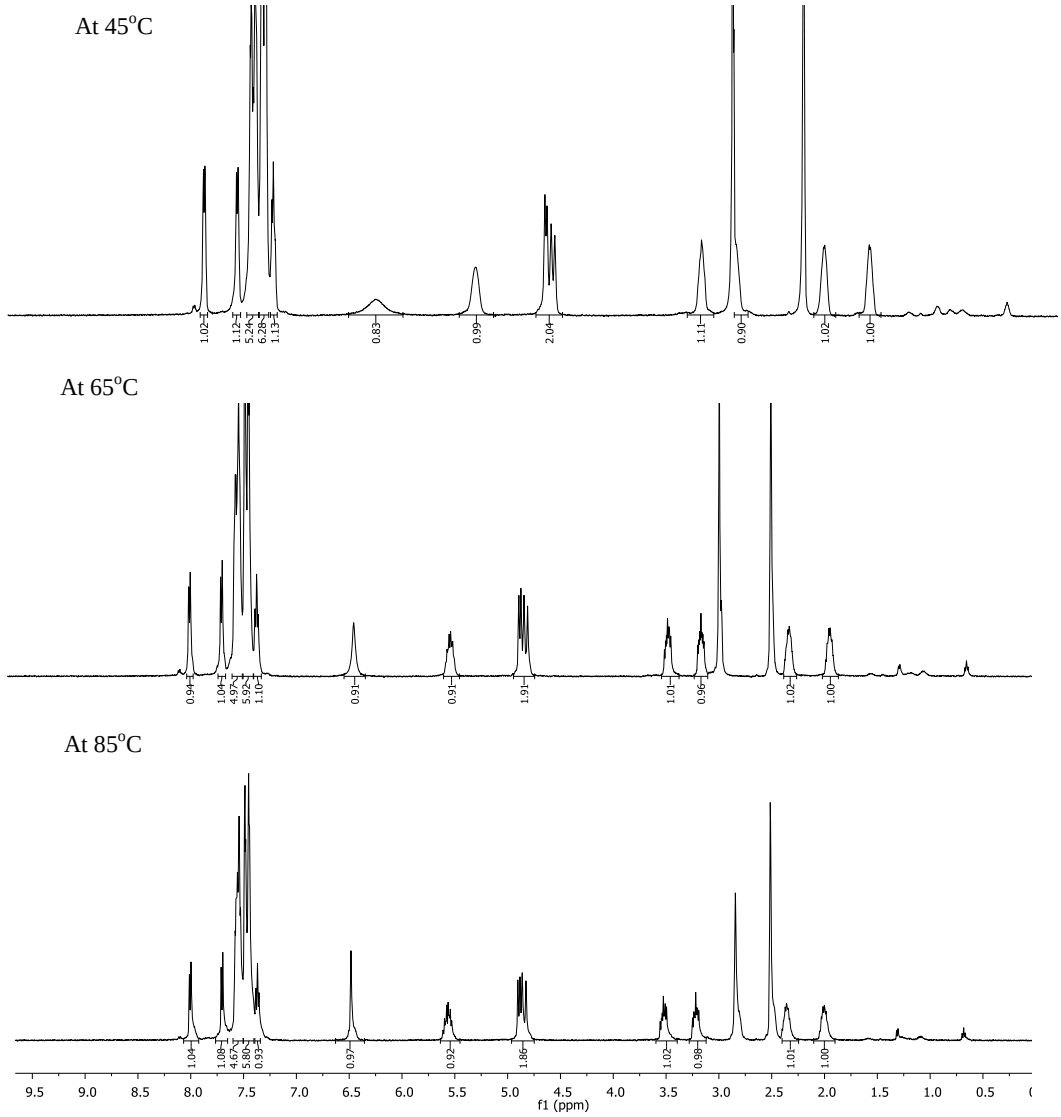


Figure 4



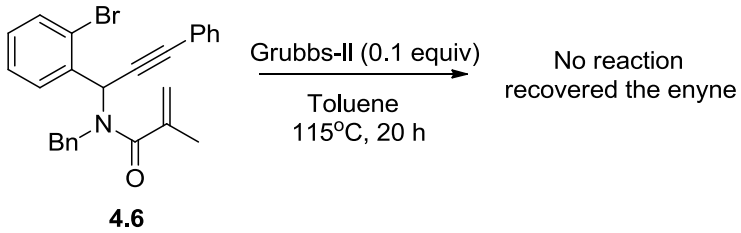


4.1.2 **Investigation of RCEYM**:

***1,6- enyne series*:**

Enyne **4.6** was treated with Grubbs II catalyst and did not afford any product, and was recovered (Scheme 4.7). This is potentially due to the sterically hindered and electronically deficient ene component which makes the enyne less favorable to coordinate with the metal center.

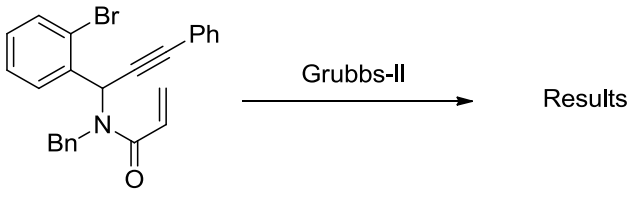
Scheme 4.7



4.6

So enyne **4.5** with sterically accessible ene component was used as the model system for the investigation of RCEYM. The initial study with Grubbs II catalyst and DCM as the solvent at 40^{o}C did not afford any product and the enyne was recovered (entry 1, Table 4). A similar result was observed at elevated temperature of 80^{o}C and toluene as the solvent (entry 2). At 115^{o}C the starting material was consumed and the reaction produced multiple products as analyzed by TLC. Only less than 20% yield of crude product was isolated, probably due to polymerization of the enyne (entry 3). Maintaining the temperature between 100-110^{o}C and increasing the catalyst loading did not improve the reaction.

Table 4



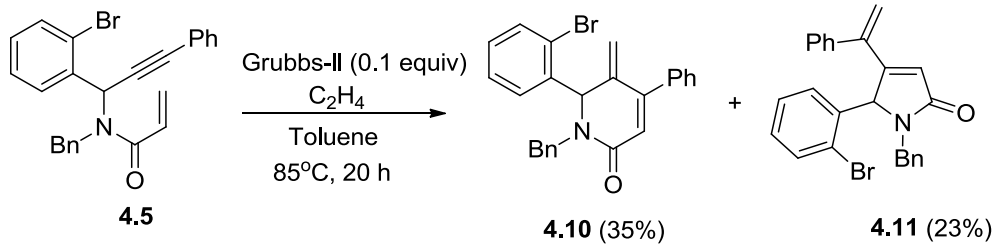
4.5

Entry	Reaction conditions	Catalyst (equiv)	Results
1	DCM, 40^{o}C, 20+15 h	0.2	Recovered starting material (SM)

2	Toluene, 80°C, 20 h	0.05	Recovered SM
3	Toluene, 115°C, 18 h	0.06	No SM, TLC-multiple spots GCMS shows mass. NMR complicated. Yield<20%
4	Toluene, 100°C, 20 h	0.1	No SM, TLC-multiple spots
5	Toluene, ethylene atm, 85°C, 20 h	0.1	Clean reaction; observed distinct spots on TLC and no streak of line

Mori and coworkers[95] reported RCEYM under ethylene atmosphere which proved to be critical for success of the reaction. Therefore, we ran our model reaction under ethylene atmosphere (entry 5) as follows: The solution of enyne **4.5** in toluene was degassed with ethylene for 5 min. and solid Grubbs II catalyst (0.1 equiv) was added. The reaction mixture was stirred at 85°C under ethylene atmosphere. After 20 h, TLC analysis showed complete conversion and formation of two new spots. The mixture was cooled to rt and directly loaded on a silica column and purified by flash chromatography, eluting with EtOAc/Hexane. The reaction furnished two isomeric products piperidone **4.10** and pyrrolidinone **4.11** (Scheme 4.8).

Scheme 4.8



4.5

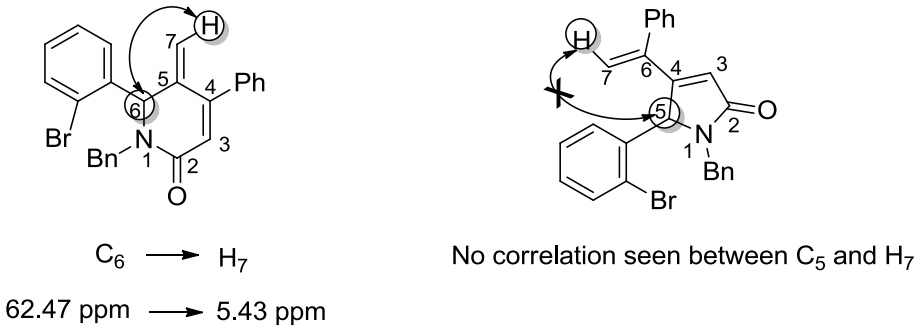
4.10 (35%)

4.11 (23%)

The poor selectivity is due to the presence of electron deficient olefin which slows down the coordination of enyne through the ene component with the metal center and allowing the yne component to initiate the reaction. Formation of piperidone can be explained via yne-then-ene pathway wherein the coordination of enyne with the metal center is initiated by the yne component. The formation of pyrrolidone can be explained via ene-then-yne pathway wherein the coordination of enyne with the metal center is initiated by the ene component (Section 2.3.2 *vide supra*).

The major and minor product assignment was successfully achieved using HMBC (Figure 5). In piperidone we see a three bond correlation between methine carbon C6 (62.47 ppm) and the methylene proton H7 (5.43). But in pyrrolidinone this interaction is a four bond correlation and is not observed

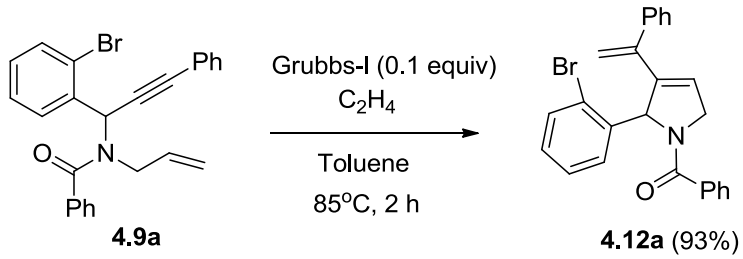
Figure 5



We envisioned transposition of the amide carbonyl away from the olefin would provide us with a more reactive enyne. As expected, enyne **4.9a** when treated with of Grubbs I catalyst according to procedure described for (Scheme 4.8), and for 2 h under the ethylene atmosphere underwent efficient metathesis reaction to afford diene **4.12a** in 93% yield (Scheme 4.9). Grubbs II catalyst also produced similar

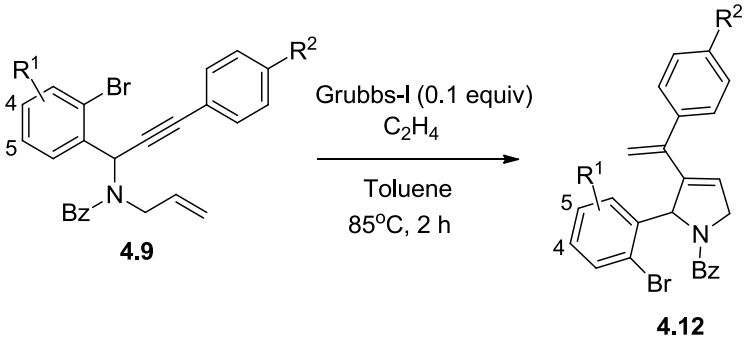
results. However, Grubbs I catalyst was used to synthesize other analogs (Table 5) as it is less expensive than Grubbs II catalyst.

Scheme 4.9



4.9a **4.12a** (93%)

Table 5

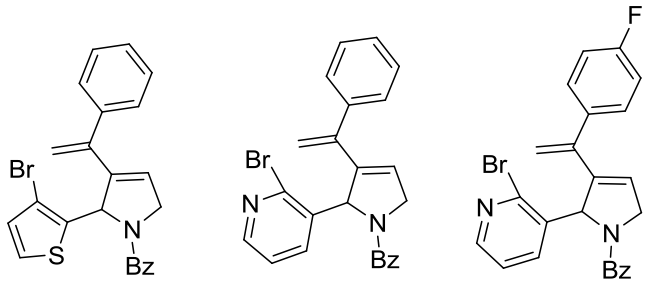


4.9 **4.12**

Entry	Enyne (4.9)	R^1	R^2	4.12 (% Yield)
1	**4.9a**	H	H	4.12a (93)
2	**4.9b**	4,5-$(OMe)_2$	H	4.12b (81)
3	**4.9c**	5-F	H	4.12c (72)
4	**4.9d**	H	F	4.12d (87)
5	**4.9e**	H	OMe	4.12e (63)

Enynes (**4.9k**, **4.9m** and **4.9n**) containing additional heteroatoms also afforded the RCM products **4.12f**, **4.12g** and **4.12h** in good yields respectively (Figure 6). Surprisingly enyne **4.9o** afforded only trace amount of RCM product and was recovered after column chromatography.

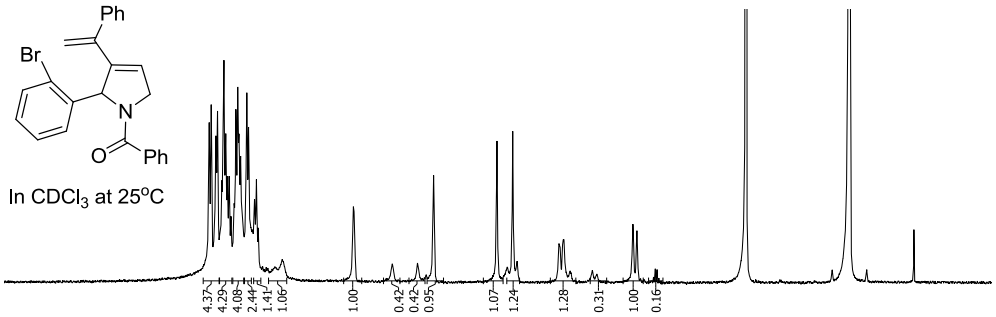
Figure 6



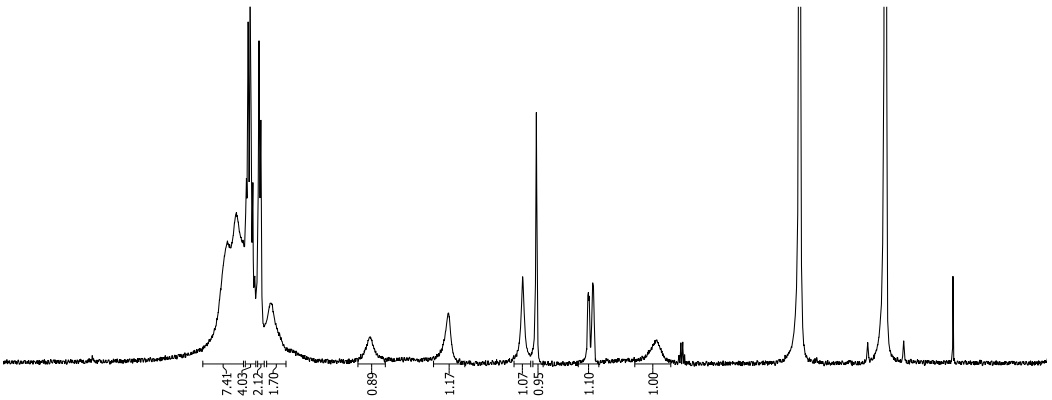
4.12f (81%) **4.12g** (80%) **4.12h** (60%)

All the **4.12** dienes proved to be somewhat unstable and were stored at below 0^{o}C and had to be used within 24 h. The ^{1}H-NMR spectra contained a few additional signals integrating for less than 1H. This is due to the restricted rotation created by the amide functional group and also due to the atropisomerism. This was proved by running temperature dependent ^{1}H-NMR spectroscopy for one of the analogs. As the temperature increased, the additional signals merged giving a proper integration value to the respective signals (Figure 7)

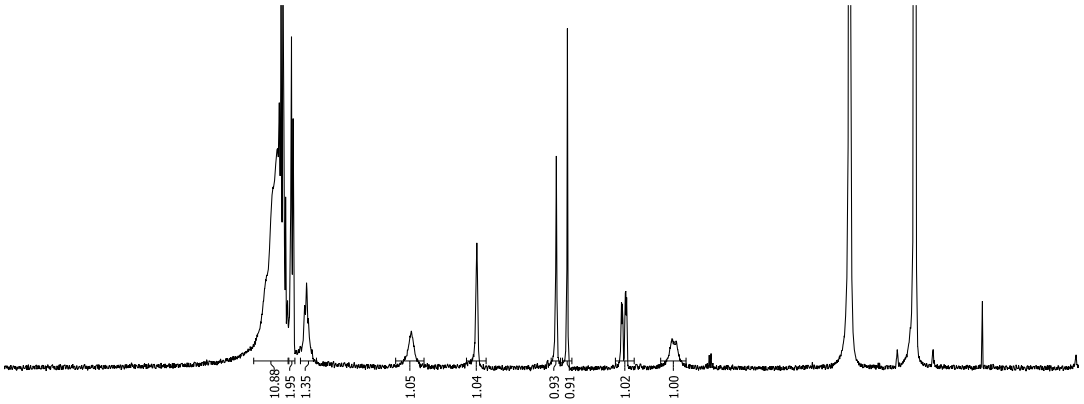
Figure 7



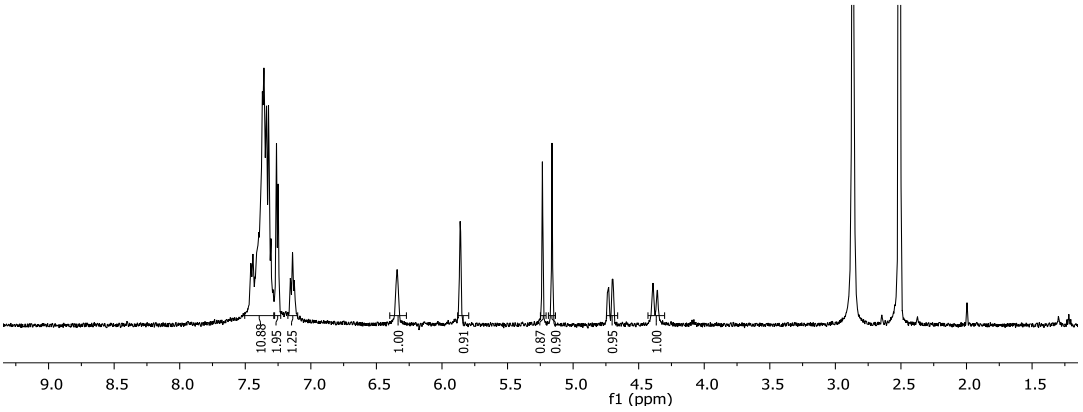
At 45°C



At 65°C



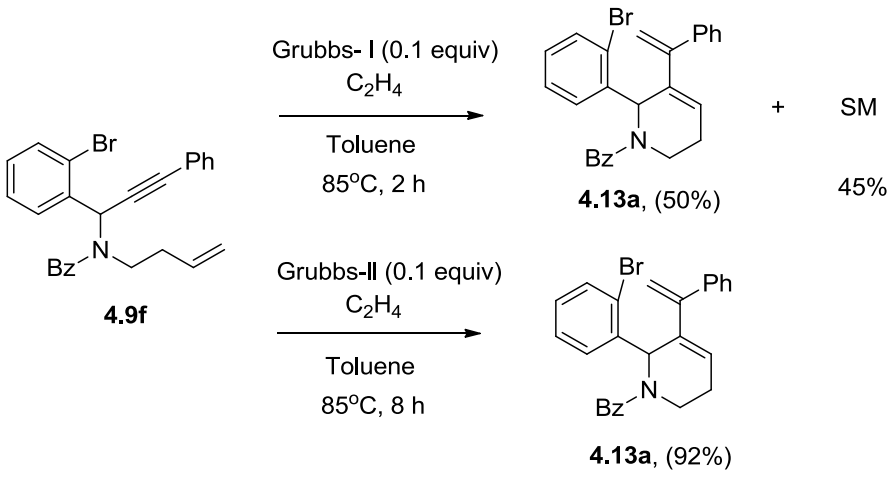
At 85^{o}C



1,7- enyne series:

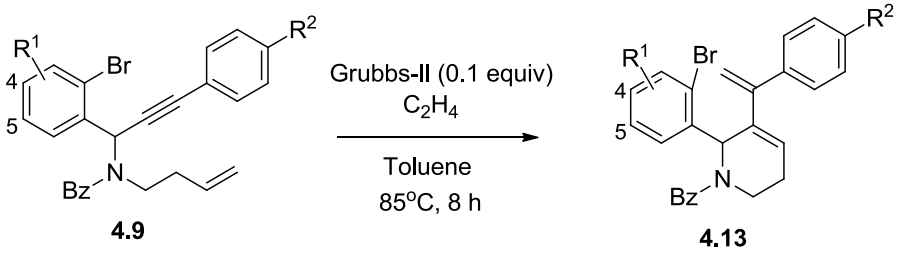
The metathesis reaction of the homologous series (1,7-enynes) under the same conditions with Grubbs I catalyst did not go to completion. However, upon using the more reactive Grubbs II catalyst and longer reaction time, the substrate underwent complete conversion affording tetrahydropyridine **4.13a** in excellent yield (Scheme 4.10).

Scheme 4.10



Using the optimized conditions of Grubbs II catalyst and longer reaction time, various analogs were synthesized. (Table 6).

Table 6.

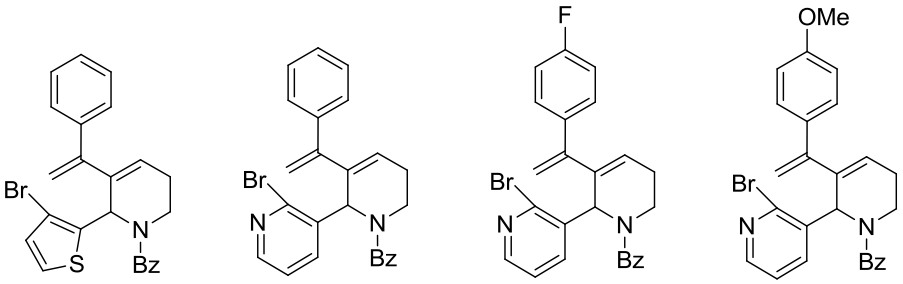


4.9 **4.13**

Entry	Enyne (4.9)	R^1	R^2	4.13 (% Yield)
1	**4.9f**	H	H	**4.13a** (92)
2	**4.9g**	4,5-$(OMe)_2$	H	**4.13b** (87)
3	**4.9h**	5-F	H	**4.13c** (88)
4	**4.9i**	H	F	**4.13d** (85)
5	**4.9j**	H	OMe	**4.13e** (80)

Enynes **4.9l** and **4.9p-r**, containing additional heteroatoms also afforded the RCM products in good yields (Figure 8). The lower yields of **4.13h** and **4.13i** are due to loss during silica column chromatography because the reaction proved to be clean based on TLC analysis.

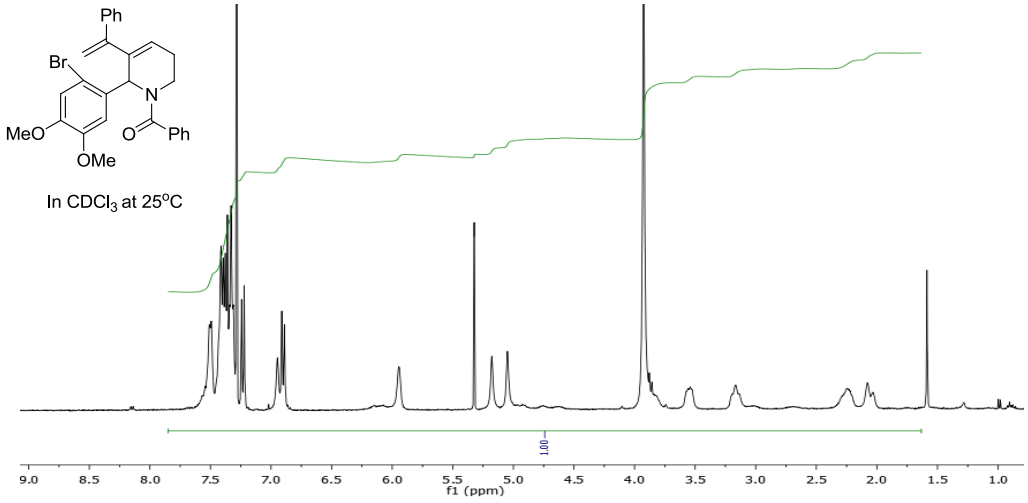
Figure 8

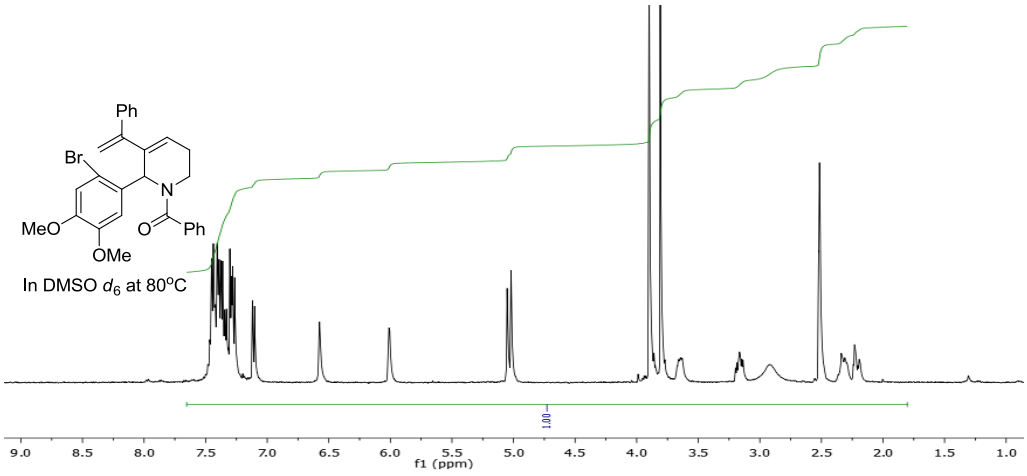


4.13f (82%) **4.13g** (84%) **4.13h** (62%) **4.13i** (58%)

The signals in ^{1}H-NMR spectra of all the **4.13** tetrahydropyridines were broad and short but had no additional signals as seen in **4.12**. Running a high temperature ^{1}H-NMR sharpened the signals considerably (Figure 9).

Figure 9

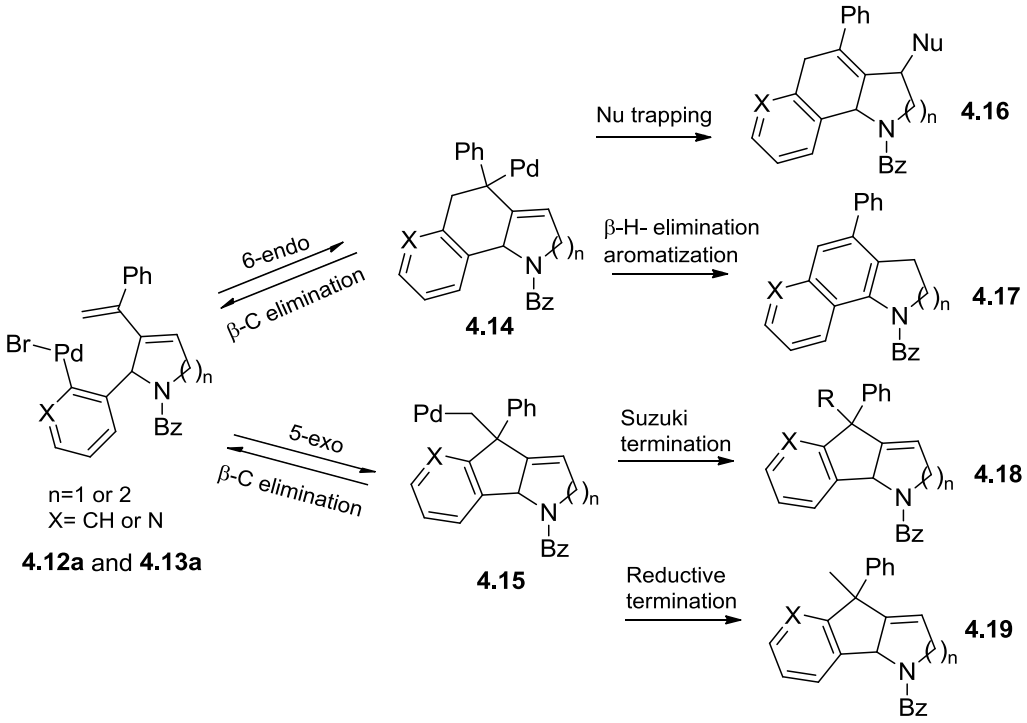




4.1.3 **Regiodivergent via 6-*endo* and 5-*exo* Heck Cyclization**

The 1,3-diene system generated by the RCEYM can be potentially used as the handle to further diversify the RCEYM products. We decided to perform an intramolecular Heck reaction using the aryl bromide motif which is already incorporated in the scaffold and the 1,3-diene as the coupling partners. This would give rapid access to a variety of fused *N*-heterocycles **4.16**-**4.19** (Figure 10) possessing drug like scaffolds[162] potentially endowed with valuable medicinal properties.[163-165] The Heck cyclization of dienes **4.12** and **4.13** may proceed via the kinetically favored 5-*exo* pathway[166] or the 6-*endo* route[166] generating an allylpalladium intermediate **4.14**.[167] Both these pathways are potentially reversible via β-carbon elimination.[168]

Figure 10

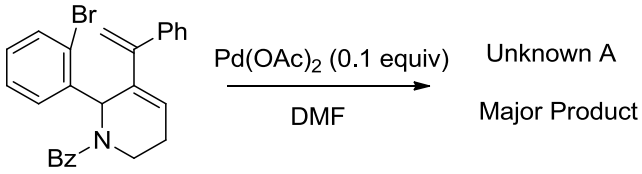


Proof of Concept:

Compound **4.13a** (n=2 and X=CH) was picked as our model system to optimize the Heck reaction (Table 7). We proposed that the reaction would favor the 5-*exo* pathway, generating **4.15** like intermediate which can be trapped via reductive Heck or by a boronic acid via Suzuki coupling (Figure 10). When the reaction was performed under the reductive Heck conditions[114] (Table 7, entries 1-3), the reaction afforded an unknown product 'A' in moderate yield. We call it unknown because the ^{1}H NMR spectrum of A did not match with the expected 5-*exo* product **4.19** (n=2 and X=CH) or with the 6-*endo* products **4.16** and **4.17** (n=2 and X=CH). The change of catalyst (entry 2) or the ligand (entry 3) did not seem to alter the reaction pathway.

Unknown A was obtained in a good yield even under the simple Heck reaction conditions (entry 4).

Table 7



4.13a

Entry	Ligand	Base	Additive	temp(^{o}C)	time	Major product[a]	yield[b] (%)
1	PPh_3	TEA	HCOOH	80	30 mins	A	60
2[c]	-	-	HCOONa	100	4h	A	65
3	Davephos	NaOAc	HCOOH	120	18h	A	
4	PPh_3	Cs_2CO_3	-	120	18h	A	80
5	-	Piperidine	-	120	24h	A	65
6[d]	PPh_3	Cs_2CO_3	-	125	18h	A	80
7	-	NaOAc	-	115	18h	A + SM	55+25

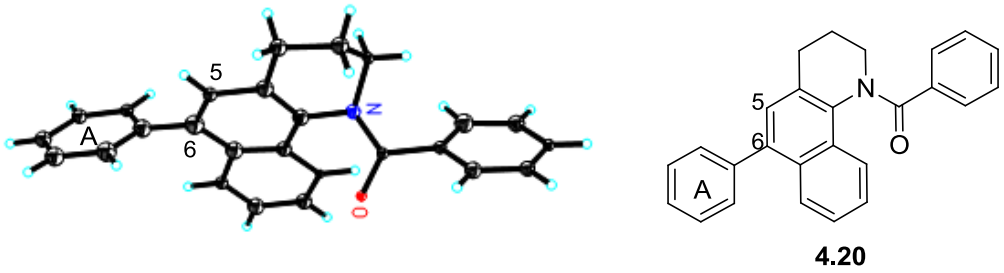
a) observed in crude H-NMR; b) isolated yield; c) used $Pd(PPh_3)_4$, DMF:H_2O 3:1; d) 10 eq of piperidine

Attempts to trap the allylpalladium complex **4.14** (n=2 and X=CH) with amine nucleophiles were not successful and once again the reaction afforded unknown A (entries 5 and 6). Under the ligandless condition (entry 7) previously reported by our group,[159] the reaction did not go to completion and afforded unknown A (55%) along with unreacted diene (25%).

In all these entries, formation of a minor product with very close R_f value to the major product was observed by TLC analysis and also in the crude ^{1}H NMR spectrum. A careful silica column chromatographic separation was needed to isolate the pure

minor product. The ^{1}H NMR spectrum of the minor product was not conclusive because the spectra featured more signals than expected, and the signals were broad. Again this could be due to the hindered rotation about the amide bond. Fortunately, X-ray quality crystals were obtained for the minor product and the X-ray structure revealed an interesting product benzoquinoline **4.20** (Figure 11).

Figure 11



4.20

At first glance the structure seemed to have formed via 6-*endo* cyclization. But the position of the aryl ring 'A' puzzled us. If the product was derived via 6-*endo* cyclization, the position of the aryl ring 'A' should have been on C-5 and not on C-6. Meanwhile we were working on the structural elucidation of the major product –the "unknown A". After a long time and with the help of 2D NMR techniques (HMBC and HSQC) the structure of unknown A was elucidated and was found to be cyclopropane fused indenopyridine **4.21a** (Scheme 4.11). The structure and the relative stereochemistry was further confirmed by X-ray crystallographic analysis of one the analogs **4.21b** (Figure 12).

Scheme 4.11

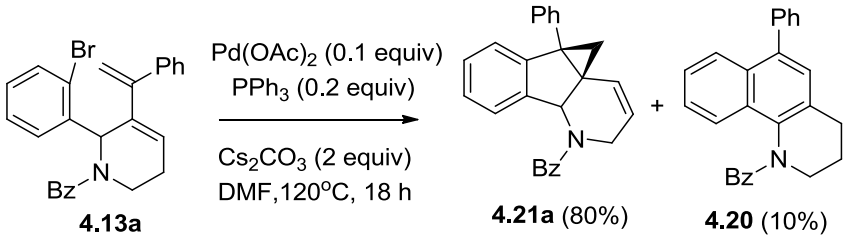
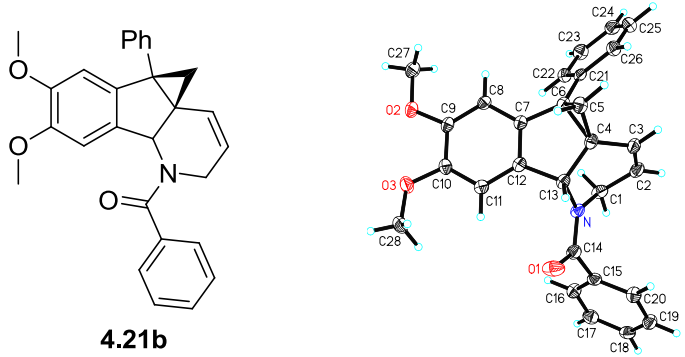


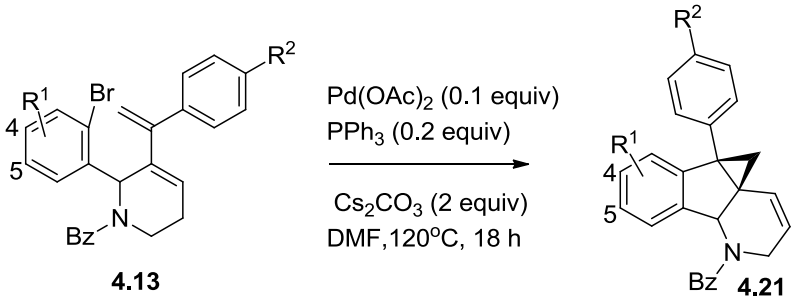
Figure 12



The optimized conditions for the production of "unknown A" proved to be entry 4, Table 7. Various analogs were synthesized to explore the substrate scope of the reaction (Table 8). Incorporation of electron donating or electron withdrawing groups in R^1 and R^2 position did not seem to change the regioselectivity of the reaction. In all the cases, the 5-*exo* regioselectivity of the Heck annulation uncovered in the original studies was followed. Thus no electronic effects of the substituents on the course of the Pd-catalyzed annulations were detected. The ^{1}H NMR analyses of crude reaction mixtures from the reactions providing indenopyridines **4.21b-e** indicated the presence (less than 10%) of benzoquinoline byproducts analogous to heterocycle **4.20** (Scheme 4.11). They were easily separated by column chromatography. Except for heterocycle **4.20** others were not isolated pure or

characterized. The relative stereochemistry in indenopyridine series wase established by X-ray crystallographic analysis, utilizing an indenopyridine analogue **4.21b** prepared as shown in (Table 8). All the analogs were stored in refridgerator and seemed to be stable.

Table 8



Entry	Diene (4.13)	R^1	R^2	4.21 (% Yield)
1	**4.13a**	H	H	**4.21a** (80)
2	**4.13b**	4,5-$(OMe)_2$	H	**4.21b** (78)
3	**4.13c**	5-F	H	**4.21c** (71)
4	**4.13d**	H	F	**4.21d** (81)
5	**4.13e**	H	OMe	**4.21e** (80)

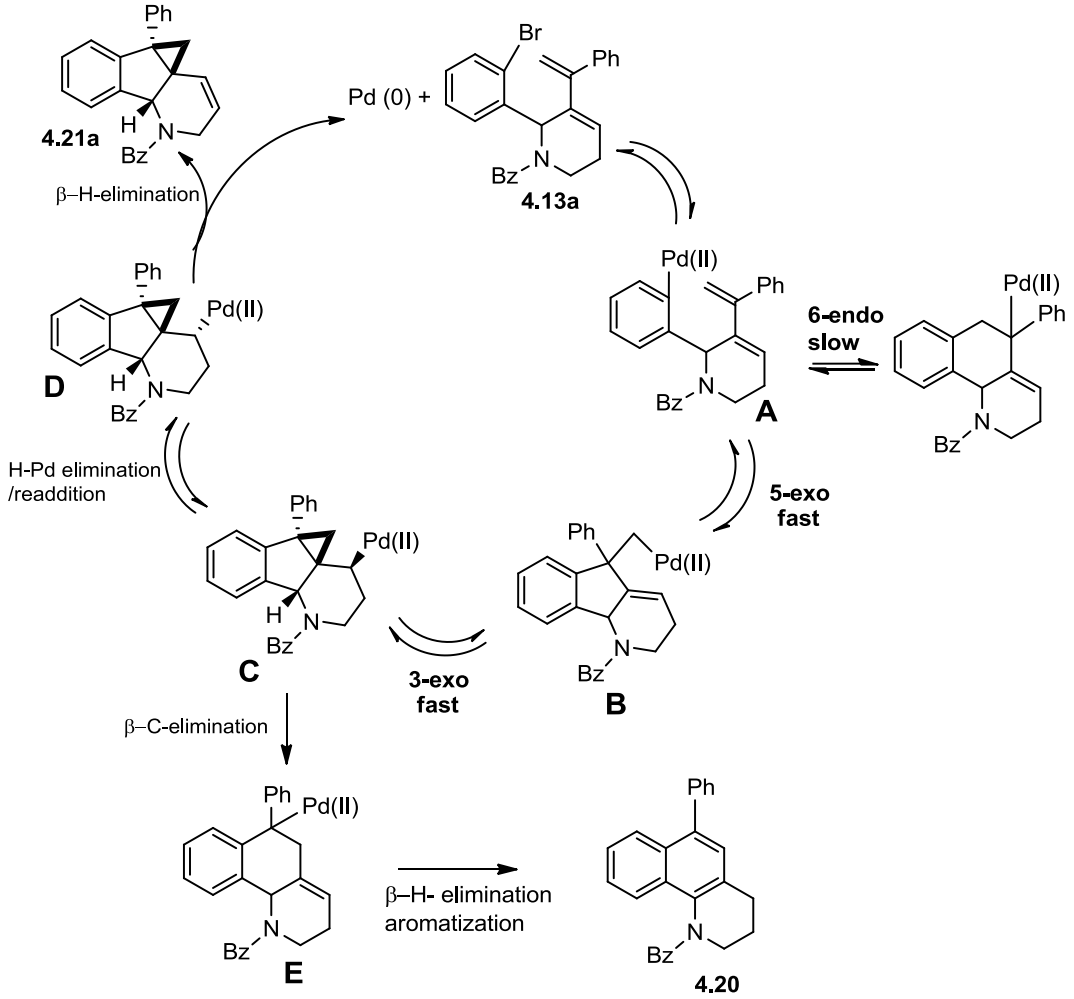
Despite running the reaction under various conditions: reductive conditions, ligandless conditions, in presence of ligand (Table 7), the reaction afforded 5-*exo* cyclized product. Therefore we believe that the formation of **4.21** from **4.13** is a substrate controlled reaction. To understand if the conformational change in the piperidine ring had any effect on the regiochemistry we synthesized the pyran analog

4.42 (Scheme 4.41 *vide infra*), which too underwent 5-*exo* cyclization to produce cyclopropane fused indenopyran scaffold **4.43** (Scheme 4.41 *vide infra*).

Proposed Mechanism

Based on the structures formed in the Heck reaction, we propose the following mechanism for the formation of cyclopropane fused tetrahydroindenopyridine (Scheme 4.12).

Scheme 4.12



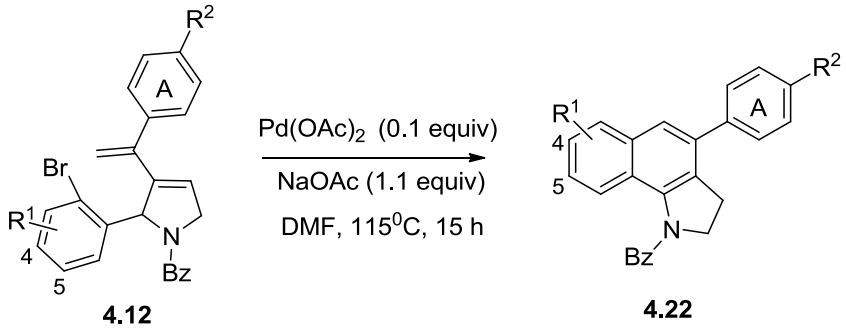
The intermediate **A** formed by oxidative addition of the Pd(0) catalyst with compound **4.13a**, undergoes kinetically favored 5-*exo* cyclization[166] affording the intermediate **B**. We believe the alternate 6-*endo* path is disfavored due to its slower reaction rate as compared to the 5-*exo* cyclization. The intermediate **B** rapidly undergoes a diastereoselective 3-*exo* cyclization giving rise to the cyclopropane ring[169-170], intermediate **C**. The intermediate **C** upon β-H-elimination followed by readdition of H-Pd(II) to the olefin forms intermediate **D**. β-H-elimination of the intermediate **D** delivers observed cyclopropane fused tetrahydro indenopyridines **4.21a**. We propose that the formation of the minor product-benzoquinoline **4.20** is due to β-C-elimination of intermediate **C** to form intermediate **E**, followed by β-H-elimination and aromatization delivers the observed benzoquinoline **4.20**.

Heck cyclization of pyrrolidines series

Excited with this unexpected outcome during Heck cyclization of tetrahydropyridine dienes **4.13**, we were curious to study and extend this protocol to pyrrolidine dienes **4.12**. Surprisingly, diene **4.12a** followed the 6-*endo* pathway when treated either with ligandless catalyst (as in Table 8, entry 7) or with the added phosphine (entry 2) affording benzoindoline **4.22a** in good yields (Table 9). Not much of optimization was done with dienes **4.12**. However the ligandless conditions were employed to study the substrate scope because, addition of fewer number of reagents would be more practical during library synthesis. The varied substituents of electron donating and electron withdrawing at R^1 and R^2 positions did not seem to alter the course of the reaction. In all the cases the regioselectivity of 6-*endo*

uncovered in the original studies was followed (Table 9). The position of the phenyl ring 'A' was confirmed by the X-ray crystallography on **4.22a**. All the analogs were stored in refridgerator and seemed to be stable.

Table 9



4.12 **4.22**

Entry	Diene (4.12)	R^1	R^2	4.22 (% Yield)
1	**4.12a**	H	H	**4.22a** (71)
2	**4.12a**	H	H	**4.22a** (73)[a]
2	**4.12b**	4,5-$(OMe)_2$	H	**4.22b** (68)
3	**4.12c**	5-F	H	**4.22c** (65)
4	**4.12d**	H	F	**4.22d** (65)
5	**4.12e**	H	OMe	**4.22e** (66)

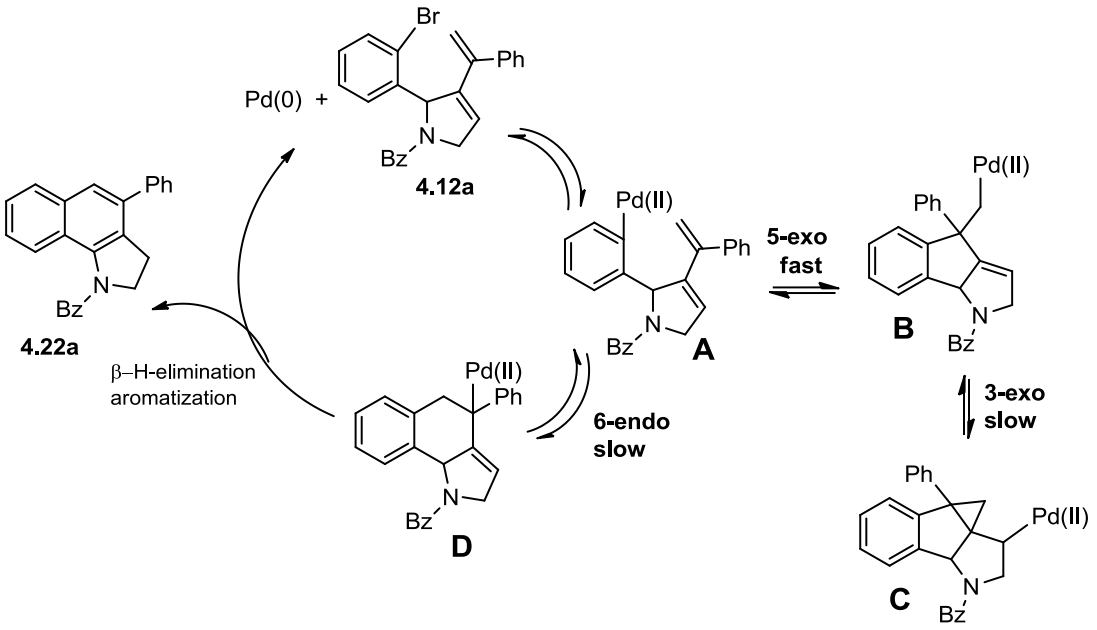
[a]Yield with $Pd(OAc)_2/PPh_3/Cs_2CO_3$

Proposed Mechanism

The formation of benzoindolines **4.22** is explained as shown in (Scheme 4.13). The intermediate **A** can undergo a kinetically controlled 5-*exo* cyclization. However the subsequent 3-*exo* cyclization of the intermediate **B** generates product with 5-5-3

fused system **C**. We believe, due to the conformational strain involved in the formation of fused 5-5-3 system, intermediate **C** reverts back to intermediate **A** and proceeds through 6-*endo* pathway to form the intermediate **D**. The intermediate **D** upon β-hydride elimination and aromatization delivers observed benzoindolines **4.22**.

Scheme 4.13



Dienes with heteroaromatic rings

With this success of eventful Heck reaction on dienes **4.12** and **4.13**, we wanted to extend it to heteroaryl dienes (Figure 6 and Figure 8) and explore if the additional heteroatom had any role in controlling the regioselectivity of the Heck cyclization. Also, incorporation of additional heteroatoms in the scaffolds would be desirable from medicinal chemistry point of view. Thus the diene with a thiophene ring **4.13f** was subjected to Heck conditions. Interestingly it did not undergo any

reaction and was recovered (Scheme 4.14). We believe it could be due to the poisoning of Pd catalyst via chelation by sulphur and amide oxygen (Figure 13).

Scheme 4.14

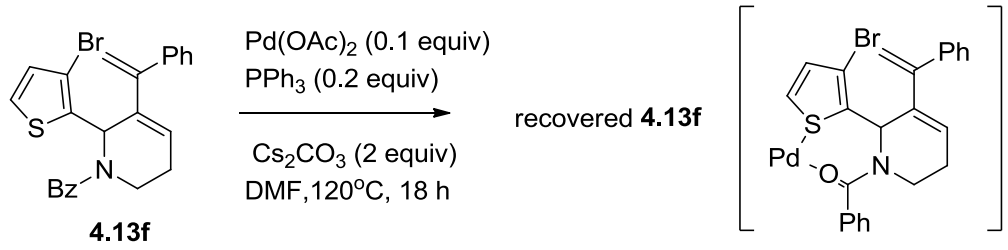
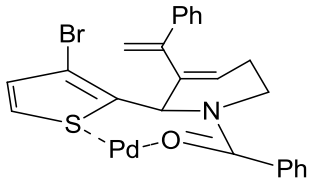
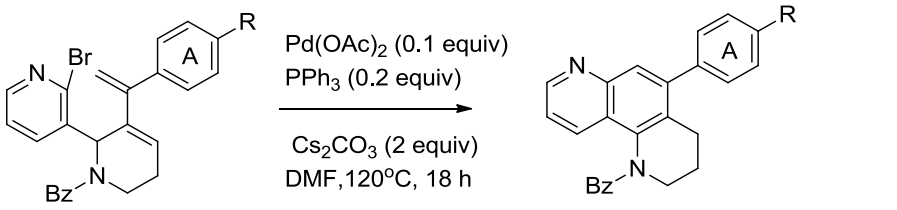


Figure 13



On the contrary, dienes with pyridine rings **4.13g-i** afforded quinolines **4.23a-c** respectively via 6-*endo* cyclization in moderate yields when treated under [$Pd(OAc)_2/PPh_3/Cs_2CO_3$] (Scheme 4.15). To asses if the choice of reagents effected the regiochemistry of Heck cyclization, diene **4.13g** was subjected to the ligandless condition [$Pd(OAc)_2$, NaOAc]. Once again the reaction produced quinoline **4.23a** in 49% yield, but the reaction did not proceed to complete conversion with 25% of starting material recovered.

Scheme 4.15



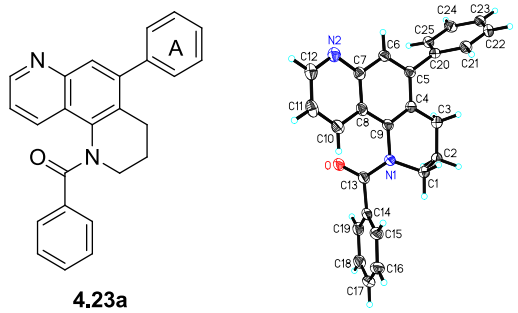
R=H **4.13g**
R=F **4.13h**
R=OMe **4.13i**

R = H **4.23a** (65%)
R = H **4.23a (**49% + SM 25%)[a]
R = F **4.23b** (61%)
R = OMe **4.23c** (59%)

[a]Yield with $Pd(OAc)_2$,NaOAc, DMF, 120°C, 18 h

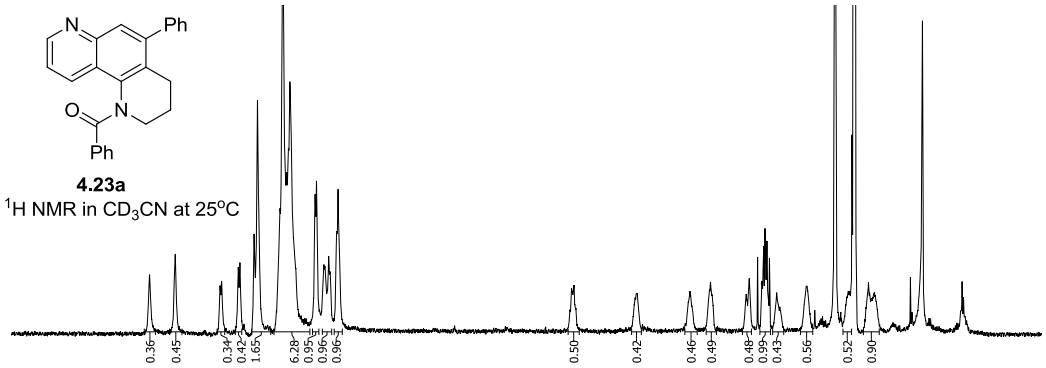
Electron withdrawing and donating substituents on ring 'A' **4.13h** and **4.13i** respectively afforded corresponding quinolines **4.23b** and **4.23c** in moderate yields. Thus the regiochemistry was unaffected by the substituents on ring A. Looking closely at this reaction, it is apparent that the 5-*exo* cyclization pathway was suppressed by the dienes with pyridine ring. This was unlike their isostere dienes **4.13a-e** (X=N vs CH) which afforded cyclopropane fused tetrahydro indenopyridines via 5-*endo* cyclization and diene **4.13f** did not furnish any product. The structures of phenanthrolines **4.23a-c** were assigned by NMR spectroscopic analysis. Most importantly, the position of the phenyl ring 'A' was unequivocally assigned by X-ray crystallography on compound **4.23a** (Figure 14).

Figure 14

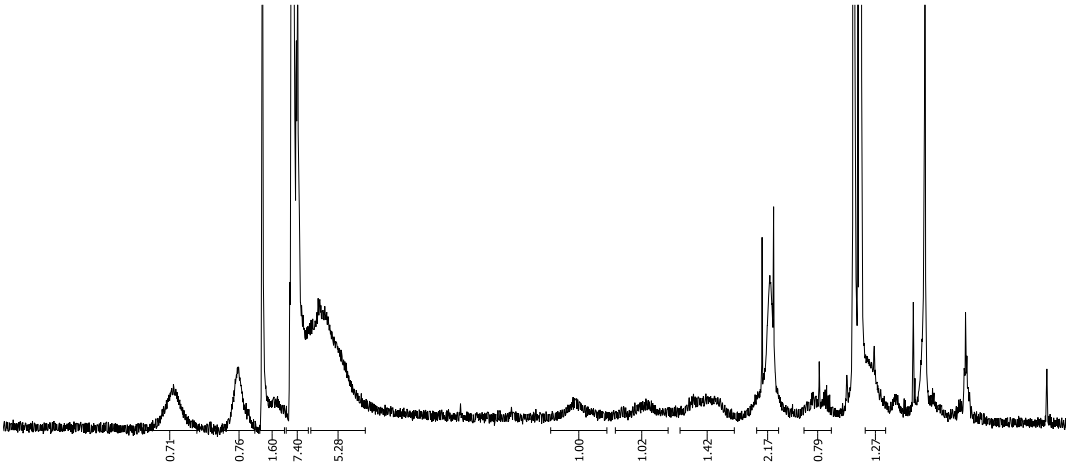


The ^{1}H NMR spectra of quinolines resembled that of benzoquinoline **4.20**. Along with spectral signals being broad and short, the spectra contained additional signals that integrated for less than 1H (Figure 15). Running ^{1}H NMR spectra of quinoline **4.23a** at elevated temperatures, the additional signals merged to provide required integration values.

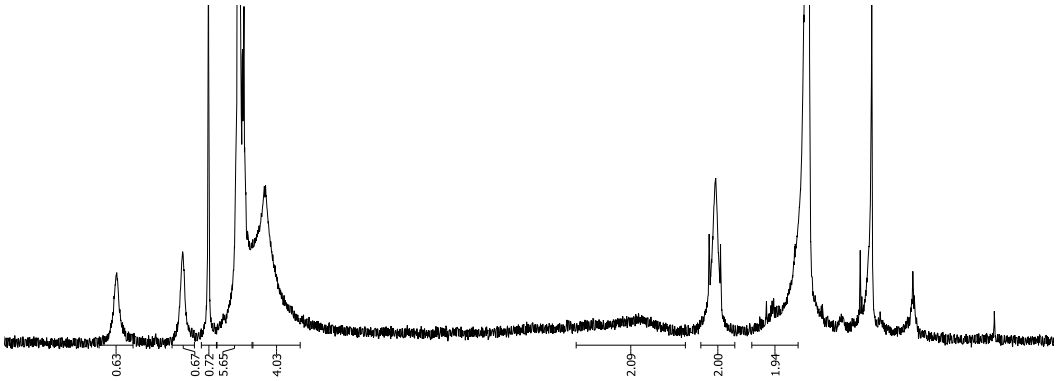
Figure 15



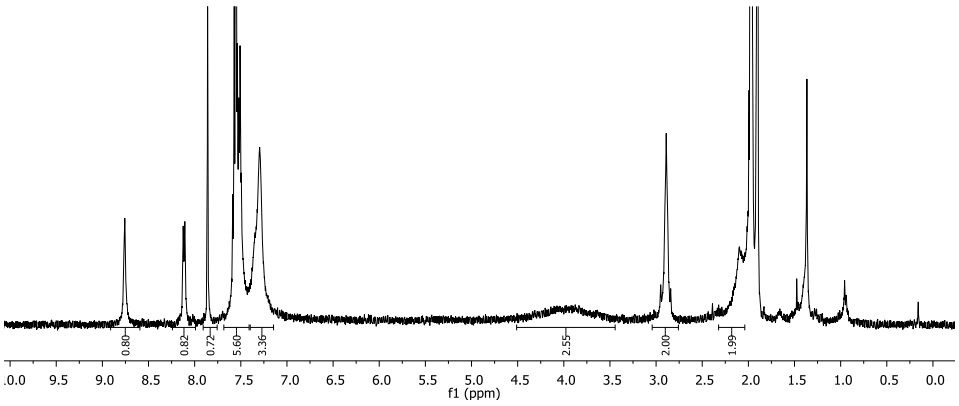
At 50^{o}C



At 65^{o}C



At 75^{o}C



The heteroaryl containing pyrrolidine dienes **4.12f-h** (Figure 6) followed the 6-*endo* pathway (Scheme 4.16 and 4.17) just like their isosteres (X=CH) dienes **4.12a-e**. The diene **4.12f** afforded pyrrolo benzothiophene **4.24** (Scheme 4.16), but the reaction did not proceed to complete conversion and diene **4.12f** was recovered in 31% yield. This could be potentially due to poisoning of the Pd catalyst via chelation by sulphur and amide oxygen (Figure 16).

Scheme 4.16

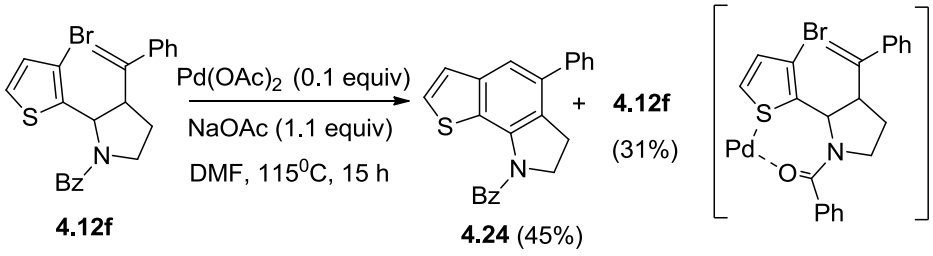
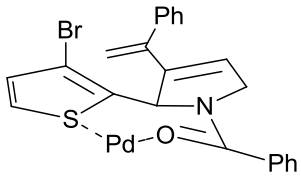
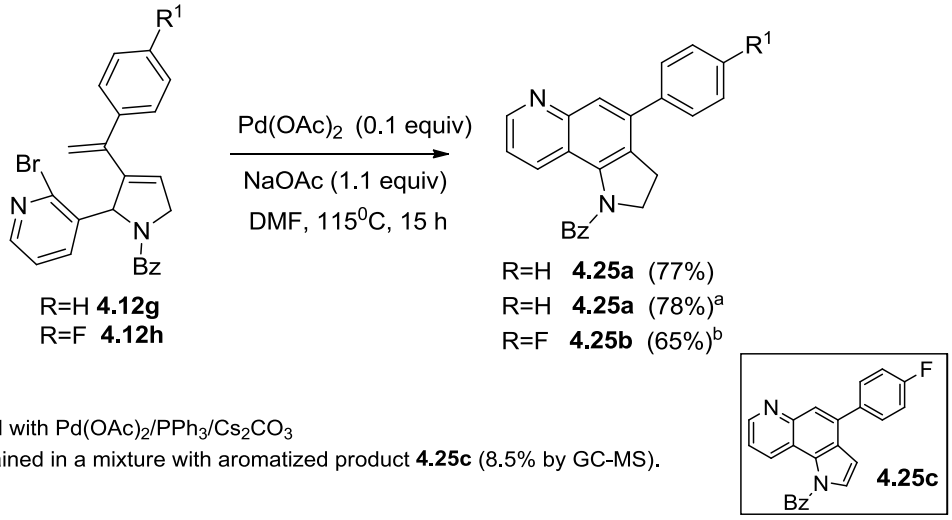


Figure 16



Diene **4.12g** furnished pyrroloquinoline **4.25a** when treated with both [$Pd(OAc)_2/PPh_3/Cs_2CO_3$] and [$Pd(OAc)_2$/NaOAc] conditions (Scheme 4.17), thus suggesting that the choice of the reagents did not affect regiochemistry of the cyclization.

Scheme 4.17



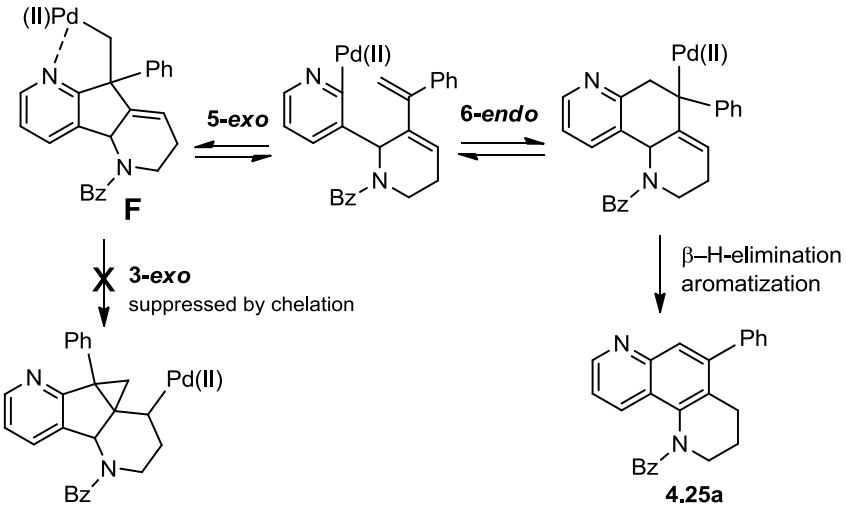
[a]Yield with $Pd(OAc)_2/PPh_3/Cs_2CO_3$

[b]Obtained in a mixture with aromatized product **4.25c** (8.5% by GC-MS).

We were concerened with the ^{1}H NMR based purity of the quinolines **4.23a-c** and dihydro pyrroloquinolines **4.25a-b**. So the purity of all these compounds were confirmed via GCMS analysis which showed acceptable purity of greater than 97% (chromatograms enclosed in appendix). However, the chromatogram of dihydro pyrroloquinoline **4.25b** (R^1=F) showed the presence of fully aromatized analog **4.25c** in 8.5% arising due to air-catalyzed oxidation of **4.25b**, facilitated by the electron deficient aromatic ring.

The anomaly observed in cyclization of pyridine dienes **4.13g-i** affording 6-*endo* product rather than 5-*exo* can be explained by the kinetic chelation trapping of the Pd(II) by the pyridine nitrogen via intermediate **F** (Scheme 4.18). As a consequence of this chelation the subsequent 3-*exo* cyclization is suppressed and the reaction reverts back to productive 6-*endo* pathway to afford phenanthroline **4.25a**.

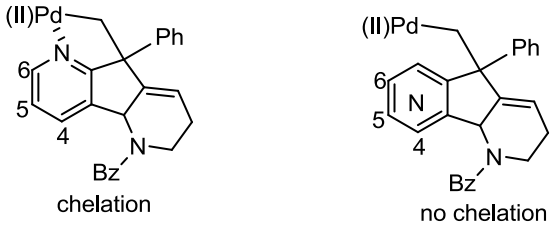
Scheme 4.18



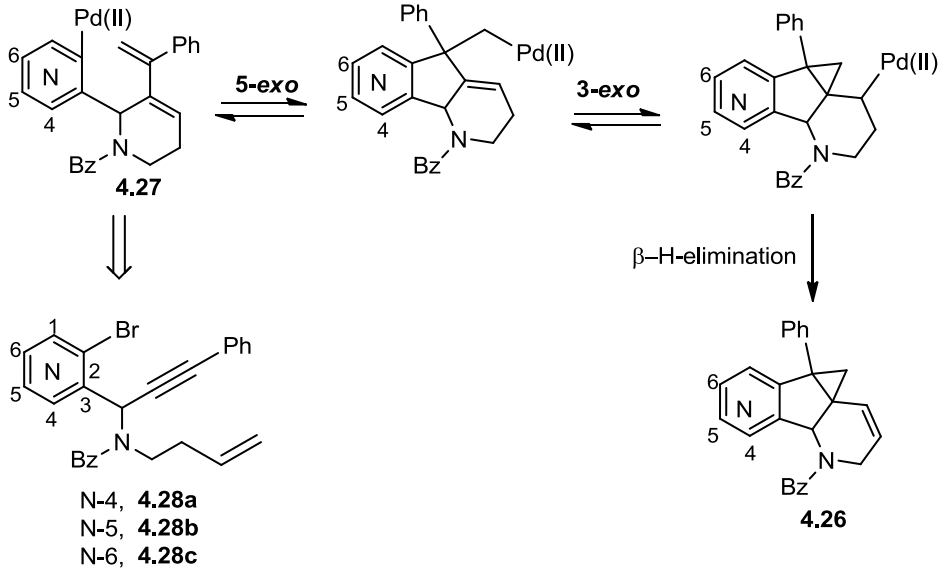
4.1.4 **Efforts Towards Synthesis of Pyridine Derivatives**:

To support our proposed mechanism of chelation-controlled synthesis of phenanthrolines, we decided to synthesize other pyridine regioisomers. We envisioned preparation of analogs with respect to pyridine nitrogen at different positions either to 4, 5 or 6 (Figure 17) should overcome the chelation of Pd catalyst with the pyridine nitrogen and allow the subsequent 3-*exo* cyclization to furnish compound **4.26** (Scheme 4.19).

Figure 17

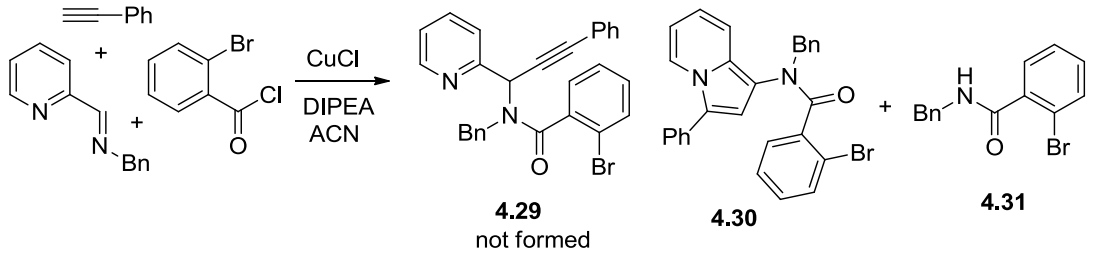


Scheme 4.19



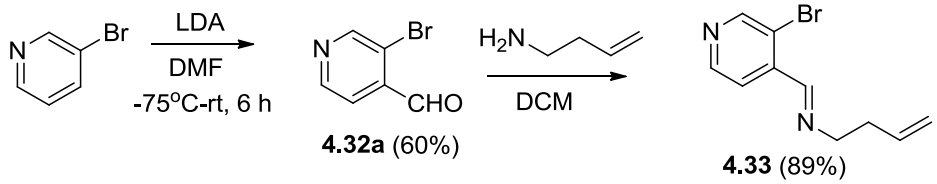
To begin with we had to synthesize corresponding dienes **4.27** which can be derived from enynes **4.28**. Dr. Sarvesh, a postdoctoral associate in Malinakova lab was working on synthesis of enyne **4.29** (Scheme 4.20), with nitrogen at C-4 as in compound **4.28a**. Unexpectedly he found that the reaction produced indolizidine **4.30** in low yield and the amide side product **4.31** as the major product formed due to premature hydrolysis of the *N*-acyliminium ion. He did not observe any formation of the desired enyne **4.29**. Thus we learned that the Cu-catalyzed MCR was not suitable for the synthesis of enyne **4.28a** with nitrogen at C-4 position.

Scheme 4.20



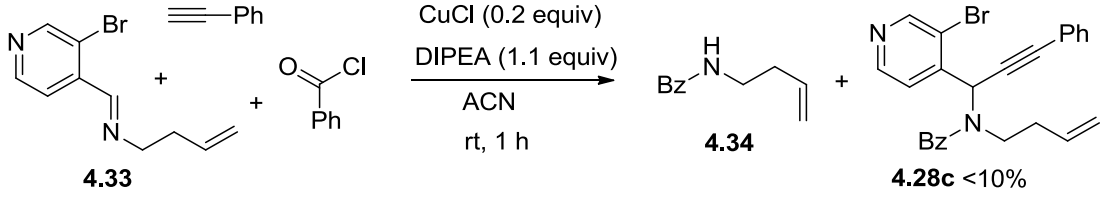
Next I directed my efforts to synthesize enyne **4.28c** with nitrogen at C-6 position. The aldehyde **4.32a** needed to synthesize corresponding imine **4.33** was prepared in gram scale using lithiation chemistry as reported in the literature (Scheme 4.21).[171]

Scheme 4.21

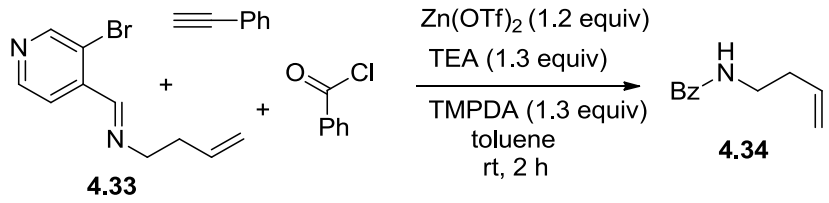


Unfortunately, the synthesis of enyne **4.28c** could not be achieved either by Arndtsen's Cu-catalyzed MCR (Scheme 4.22) or by Carreira'a Zn-catalyzed[172] MCR (Scheme 4.23). In both the cases the amide side product **4.34** formed due to premature hydrolysis of the *N*-acyliminium ion was obtained as the major product.

Scheme 4.22



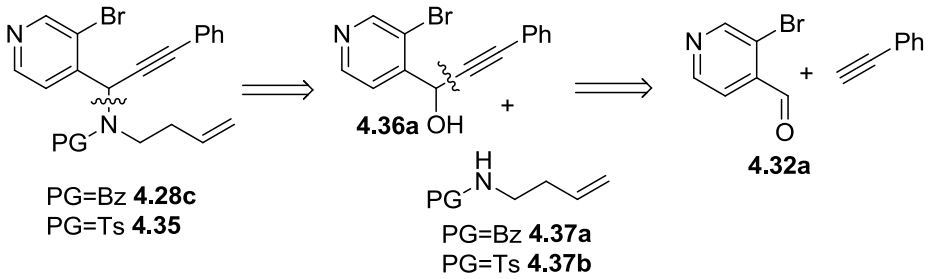
Scheme 4.23



Unable to synthesize enyne **4.28c** via MCR approach, we decided to take a stepwise approach via the propargyl alcohol precursor **4.36a** (Scheme 4.24). An S_N2

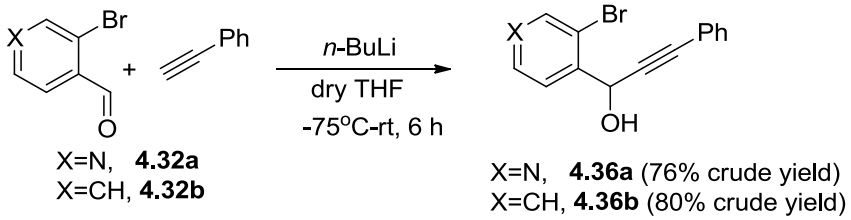
displacement of the alcohol functional group with nucleophiles **4.37a-b** would furnish the desired enynes with benzoyl protected amine **4.28c** or with tosyl protected amine **4.35**.

Scheme 4.24



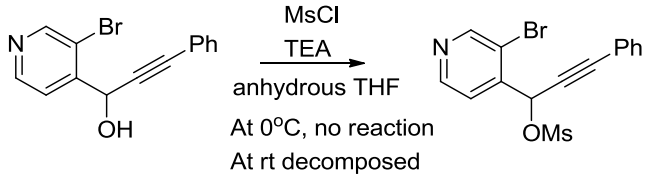
The propargyl alcohol **4.36a** was synthesized by nucleophilic attack of lithium phenyl acetylide on to the aldehyde **4.32a** (Scheme 4.25).[173-174] The solution of aldehyde in THF was added to the *insitu* generated lithium phenyl acetylide in THF at -75^{o}C. The reaction proceeded cleanly with only traces of impurities being formed as suggested by ^{1}H NMR spectroscopy of the crude reaction mixture. The crude propargyl alcohol **4.36a** was used as such for further reactions. Initially we were worried about the lithium halogen exchange problem, but we were pleased to see the aryl bromide motif remained intact.

Scheme 4.25

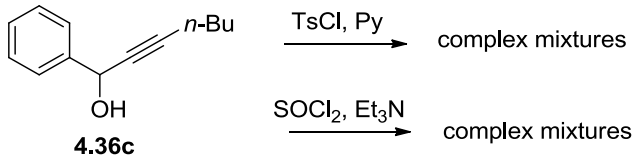


Next we envisioned to transform the alcohol group into a good leaving group such as mesylate and then perform a S_N2 displacement with the *N*-tosylamide **4.37a**. This would give us access to enyne **4.35**. Mesylation of the alcohol did not seem to progress when performed at 0°C. Warming the reaction mixture to rt decomposed the propargyl alcohol (Scheme 4.26). This observation agreed with the report by Shi and coworkers (Scheme 4.27).[175] In their attempts to functionalize the propargyl alcohol **4.36c**, they observed complex mixtures.

Scheme 4.26

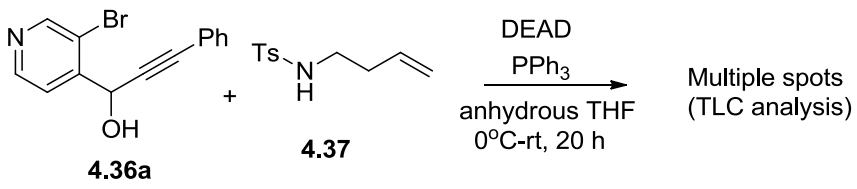


Scheme 4.27



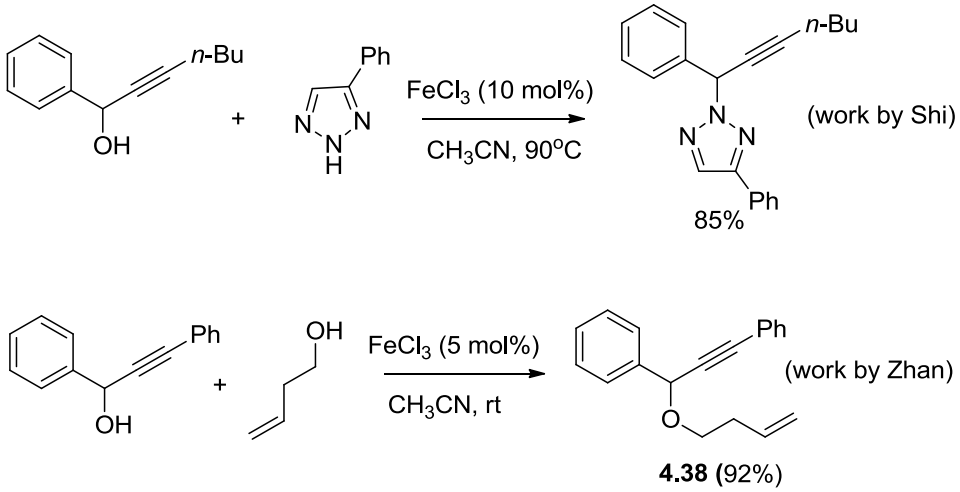
An alternate route via Mitsunobu reaction created multiple products as observed by TLC analysis (Scheme 4.28).

Scheme 4.28



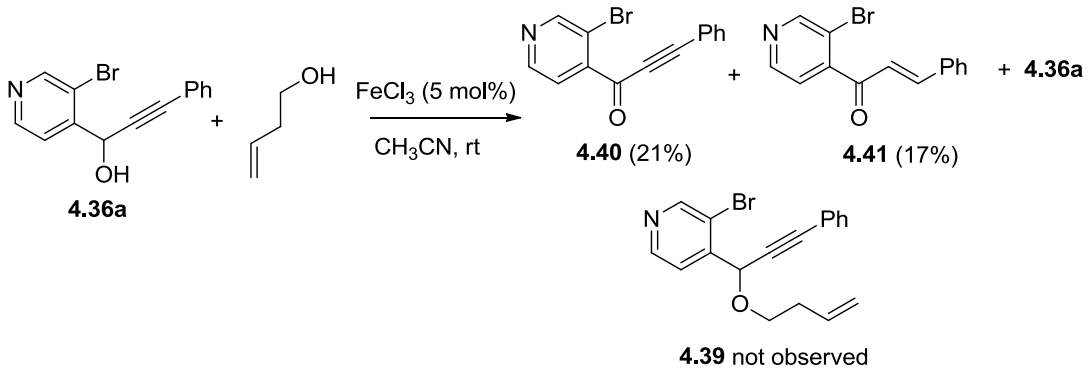
Unable to synthesize enyne **4.35** via the classical approach, we sought to use Fe-catalyzed activation of the C-O bond reported by Shi[175] and Zhan[176] (Scheme 4.29). Notice the formation of ether tethered 1,7-enyne **4.38** which could be a potential substrate for the synthesis of oxygen containing heterocycles via our sequential RCM/Heck strategy.

Scheme 4.29



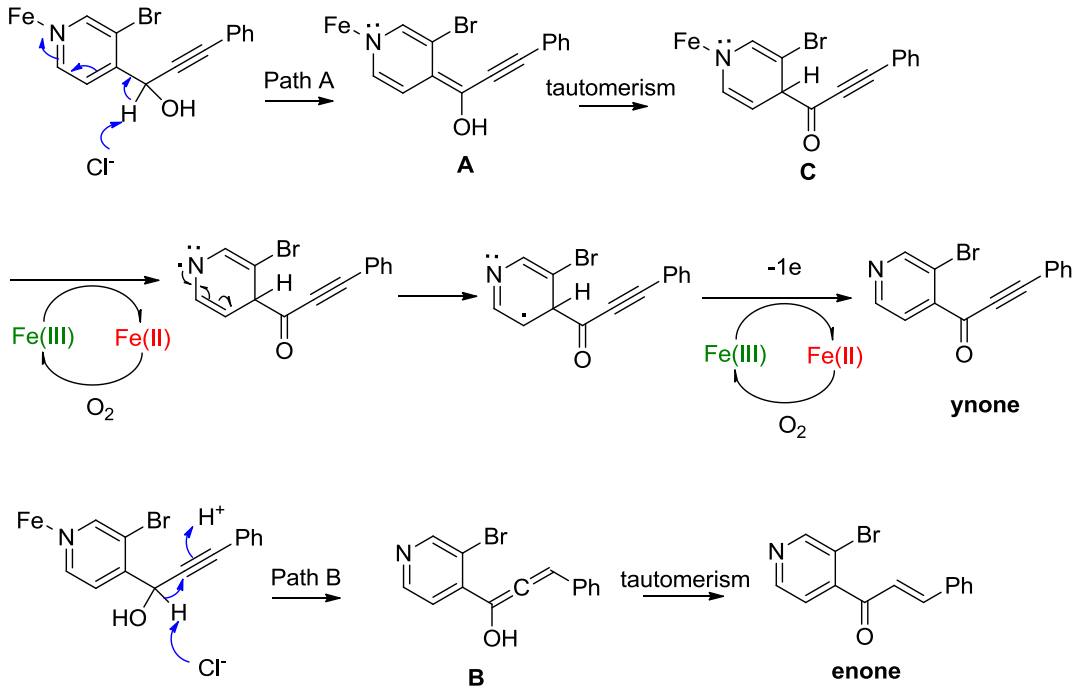
Taking inspiration from these works when the propargyl alcohol **4.36a** was treated with 4-pentenol and $FeCl_3$, the reaction produced an unexpected result. Instead of delivering the enyne **4.39** (Scheme 4.30), the reaction afforded ynone **4.40** and enone **4.41** along with unreacted **4.36a**.

Scheme 4.40



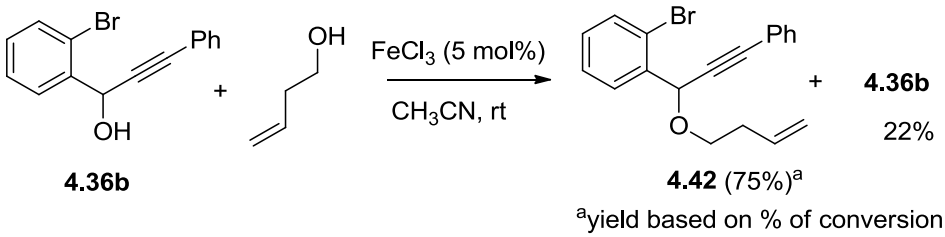
The chelation of ferric chloride activates the pyridine ring and thus increases the acidity of the propargyl proton, which upon depronation, generates enol intermediate **A** via path A or allenol intermediate **B** via path B (Scheme 4.41). The ketone intermediate **C** upon a single electron transfer oxidation followed by aromatization delivers ynone **4.40**. The allenol intermediate **B** upon tautomerization delivers enone **4.41**.

Scheme 4.41



However, unlike the pyridine propargyl alcohol **4.36a** which afforded unexpected results, propargyl alcohol **4.36b** did furnish expected enyne **4.42** along with unreacted alcohol (Scheme 4.42).

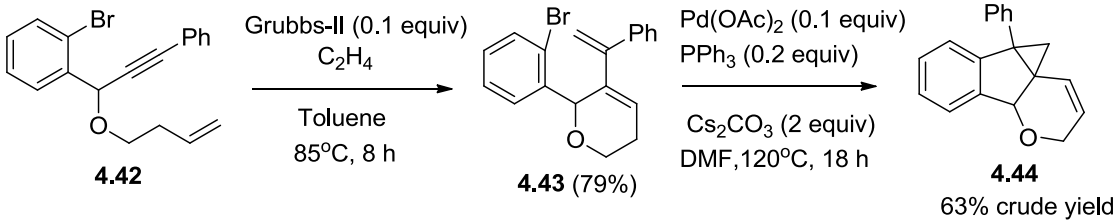
Scheme 4.42



Enyne **4.42**, when subjected to the optimized RCEYM conditions, used previously for synthesis of piperidine dienes (Table 6, *vide supra*), produced pyran **4.43** in a good yield (Scheme 4.43). With pyran **4.43** in hand we were curious if the conformational

difference between the pyran and the piperidine **4.13a** had any effect on the regiochemistry of the Heck cyclization. When the Heck reaction was performed the pyran **4.43** delivered the cyclopropane fused indenopyran **4.44** as the major product via 5-*exo* cyclization (Scheme 4.43) as analyzed from the crude ^{1}H NMR spectrum. The outcome was in agreement with the nitrogen analog-piperidine diene (NCOPh) **4.13a** (Scheme 4.11 *vide supra*). The isolation of pure **4.44** via silica column chromatography was problematic. In spite of repeated column, the compound eluted along with few close impurities. The relative stereochemistry of **4.44** is not established.

Scheme 4.43



4.2 Conclusions:

The utility of strategic sequencing of MCR with transition metal-catalyzed annulation reactions in synthesis of complex *N*-heterocycles was demonstrated.[177] The enynes generated from simple starting materials via Cu-catalyzed MCR, were converted to pharmaceutically interesting fused *N*-heterocycles by sequencing ring closing metathesis and Heck cyclization reactions. The unexpected 5-*exo* vs 6-*endo* regiodivergency during Heck annulation was uncovered affording distinct heterocyclic cores from homologous (n=1 or 2) or isosteric (X =CH or N) substrates.

The chelation trapping of the kinetic product in pyridine analogs was intriguing. A mechanism accounting for unexpected Heck cyclization was proposed.

It was experimentally concluded that the aldehyde **4.32a** was not suitable for the synthesis of cyclopropane fused pyridine analog **4.26**. This incompatibility of aldehyde **4.32a** we believe is due to *para* positioning of the pyridine nitrogen and the aldehyde functional group which facilitates hydrolysis of *N*-acyliminium ion during Cu-catalyzed MCR approach (Schemes 4.22 and 4.23) or causes side reastion in Fe-catalyzed functionalization of C-O bond (Scheme 4.40). It would be interesting to use 3-carboxyaldehyde 4-bromo pyridine and perceive synthesis of **4.26**.

Development of a sequential one-pot enyne−RCM/Heck annulation, underscoring the practicality of the new methodology will be discussed in chapter five.

Chapter Five

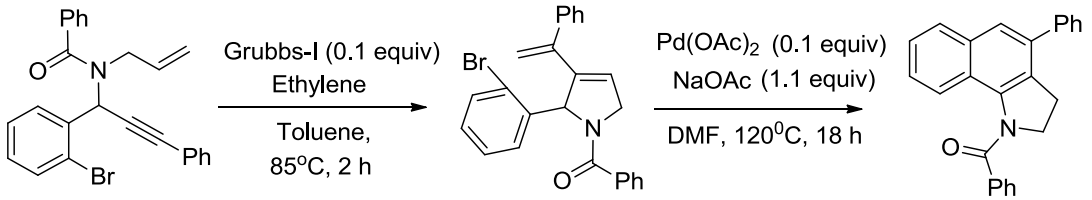
Sequential One-Pot Ring Closing Enyne Metathesis and Heck cyclization.

Ring closing metathesis and Heck reaction are two of the most powerful and widely used C-C bond forming reactions. Therefore performing them in one-pot sequences will create complex molecules with high efficiency and economy. Extensive research and explorations are being done on these two as separate reactions. However, less effort is invested in combining them as a one-pot protocol. Deriving inspiration from Grigg's work[35] (Section 2.3 chapter one *vide supra*) we decided to develop a one-pot protocol for the aforementioned RCEYM and Heck cyclization (Chapter 4 *vide supra*). This chapter describes our efforts towards this goal.

5.1 **Proof of Concept**:

We chose the two step transformation of enyne **4.9a** to benzoindoline **4.22a** as our model reaction (Scheme 5.1).

Scheme 5.1

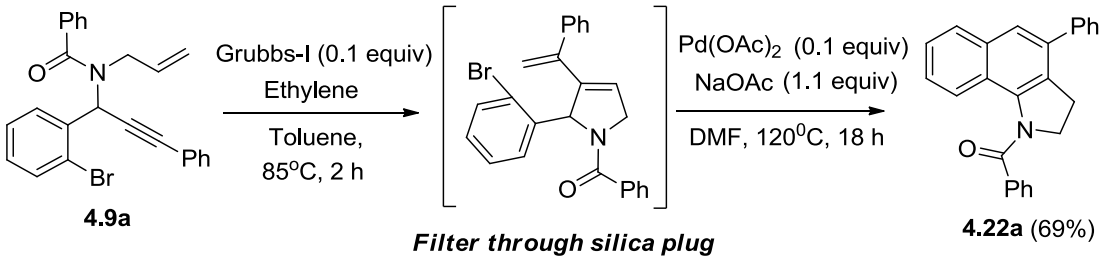


4.9a **4.12a** (93%) **4.22a** (71%)

To begin with, a simple filtration through silica plug was done after the first step of RCM. This should separate the Grubbs catalyst. The solvent (toluene) was evaporated and the crude **4.12a** was used for the subsequent Heck reaction in DMF. We were pleased to observe that even with the crude **4.12a** the Heck reaction afforded

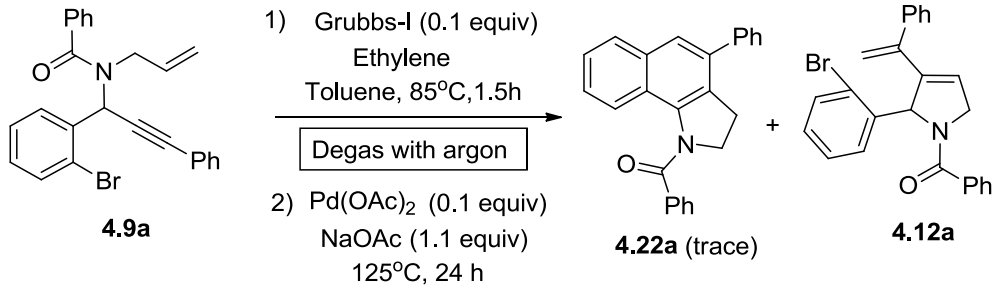
benzoindoline **4.22a** in good yield 69%, (Scheme 5.2) which was on par with the yield (71%) of the stepwise process.

Scheme 5.2



Excited with this outcome, a sequential one-pot reaction was performed as follows in toluene. After completion of the metathesis step as analyzed by TLC, the reaction mixture was cooled to rt, degassed with argon for 5 mins. and then solid $Pd(OAc)_2$/NaOAc was added and the reaction was stirred at 120 ^oC under argon atmosphere. TLC after 24 h showed most of the pyrrolidine diene **4.12a** still present and a trace of **4.22a** was formed (Scheme 5.3). Increasing the Pd catalyst loading from 0.1 equiv to 0.3 equiv did not help the cause but produced traces of multiple products.

Scheme 5.3

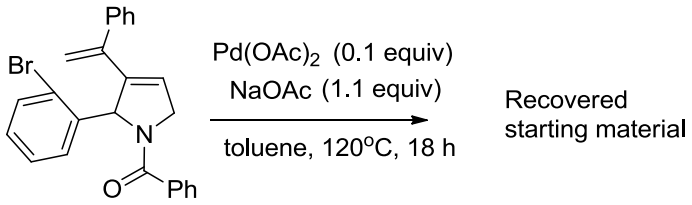


5.2 **Method optimization**:

Looking carefully at the reaction we realized that during the stepwise protocol these two reactions were being performed in two different solvents- RCEYM in toluene and Heck reaction in DMF. But in sequential one-pot reaction we had used toluene as the common solvent for both the reactions. Therefore we rationalized that the failure of sequential one-pot reaction was due to poor solubility of $Pd(OAc)_2$/NaOAc in toluene. Thus a catalytic system that could realize both the RCM and the Heck cyclizations in toluene was needed and this is when I teamed up with Monica Trejo, an undergraduate research student in our lab.

Not many metathesis friendly solvents are known, in contrast the Heck reaction can be performed in variety of solvents. So we decided not to optimize the metathesis reaction, and instead optimize the Heck reaction in toluene. Monica took up the challenge of optimizing the Heck reaction of compound **4.12a** in toluene. Just substituting toluene with DMF, did not help the cause and the starting material was recovered (Scheme 5.4).

Scheme 5.4

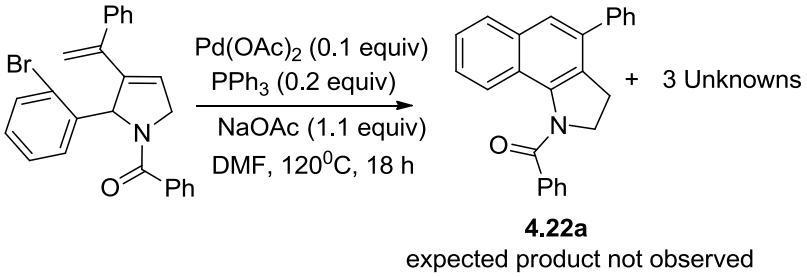


4.12a

Next she performed the reaction with added phosphine ligand to improve the solubility of Pd catalyst in toluene (Scheme 5.5). Surprisingly the reaction went to

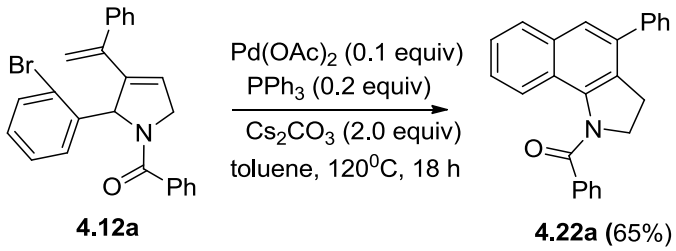
completion and produced three different products. However after purification it was found that the ^{1}H NMR spectra of all the products did not match with the expected benzoindoline **4.22a**. Repeating the reaction for second time produced same results. Nevertheless we were excited to know that the reaction has produced different products with added phosphine. The structures of the three new products have not been established yet.

Scheme 5.5



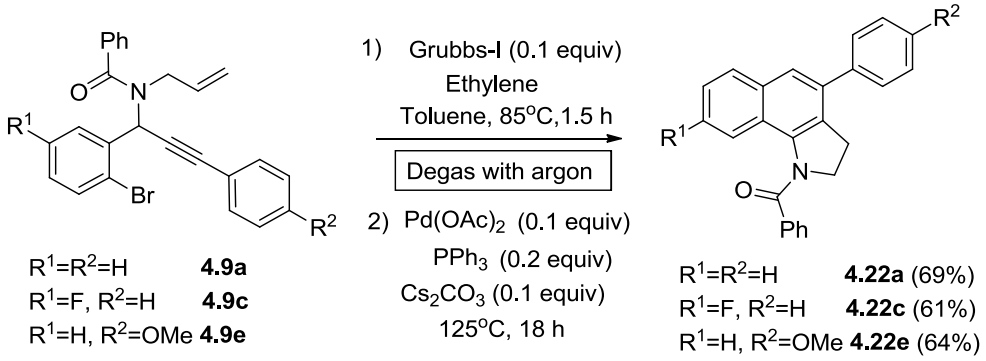
The solution to the problem of performing the Heck cyclization of pyrrolidine diene **4.12a** in toluene to afford benzoindoline **4.22a** was found when I employed the original Heck conditions [$Pd(OAc)_2/PPh_3/Cs_2CO_3$] used in synthesis of cyclopropane fused indenopyridines (Scheme 4.11 *vide supra*). Under these conditions performed in toluene, **4.12a** successfully afforded benzoindoline **4.22a** in moderate yield (Scheme 5.6).

Scheme 5.6



With this optimized result of Heck cyclization in toluene, I ventured into performing the sequential one-pot reaction in toluene. The reaction was performed on 0.18 mmol scale with respect to enyne. After completion of the metathesis reaction in toluene under ethylene atmosphere, the reaction mixture was cooled to rt and degassed with argon for 5 minutes. This saturated the reaction vessel with argon atmosphere. Then solid $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 were added one after the another and the reaction was stirred at 120^oC for 18 h. It was gratifying to see that the reaction was clean as seen from ^1H NMR of the crude mixture (Figure 1) and afforded desired benzoindolines in good yield calculated per the corresponding enynes **4.9a** after silica flash column chromatography (Scheme 5.7). The substituents and their electronics did not seem to have much effect on the yields. Analogs **4.22c** (R^1=F) and **4.22e** (R^2=OMe) were obtained in comparable yields 61-64% (Scheme 5.7). Table 1 shows percent increase in the yield via one-pot operation in comparision with the stepwise protocol.

Scheme 5.7



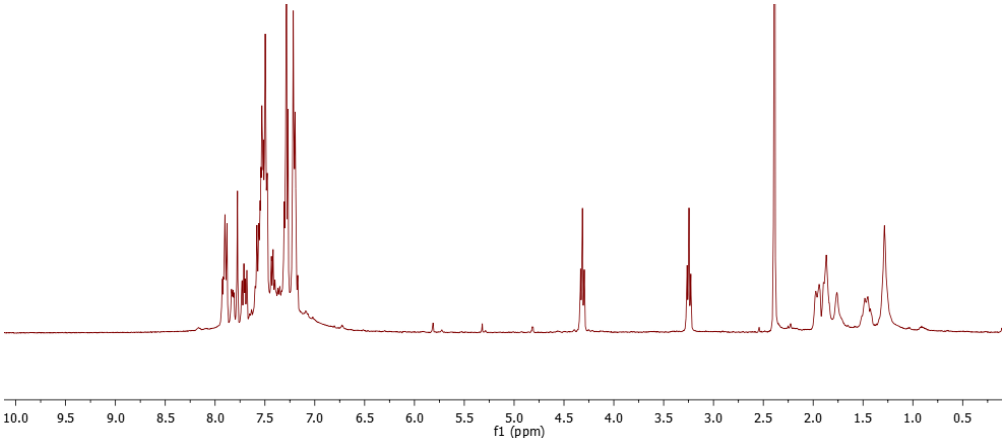
R^1=R^2=H **4.9a**
R^1=F, R^2=H **4.9c**
R^1=H, R^2=OMe **4.9e**

R^1=R^2=H **4.22a** (69%)
R^1=F, R^2=H **4.22c** (61%)
R^1=H, R^2=OMe **4.22e** (64%)

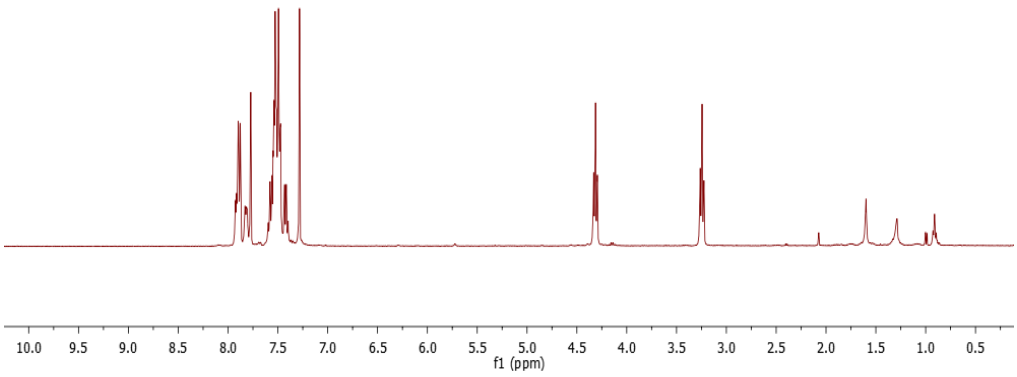
The improvement in the yields is due to overcoming the isolation and loss of metathesis product during column chromagraphy. Also it is important to note that the remains of the metathesis reagents did not alter the regiochemistry of Heck cyclization.

Figure 1

Crude reaction mixture of **4.22a** (Scheme 5.7) ^{1}H NMR in $CDCl_3$



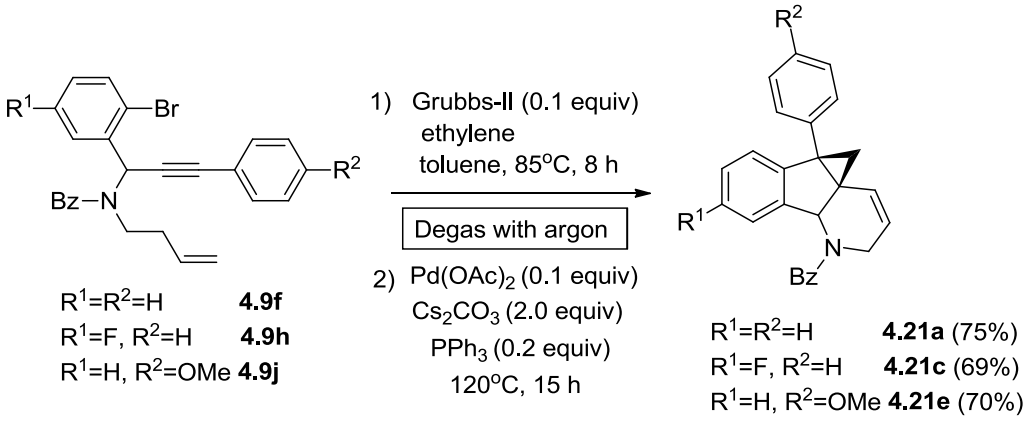
Purified **4.22a** ^{1}H NMR in $CDCl_3$



Extending the optimized sequential one-pot protocol to the homologous piperidine series also produced the desired result (Scheme 5.8). Treating enynes **4.9** sequentially with metathesis and Heck conditions afforded cyclopropane fused indenopyridines

4.21 in good yields along with the minor side product benzoquinolines **4.20**. The substituents and their electronics did not seem to have much effect on the yields and the analogs **4.21c** (R^1=F) and **4.21e** (R^2=OMe) were obtained in comparable yields 69-70% (Scheme 5.8). Table 1 shows percent increase in the yield via one-pot operation in comparision with the stepwise protocol. Once again it was gratifying to know that the reaction was clean as seen from ^{1}H NMR spectroscopy (Figure 2). Importantly the course of the Heck cyclization was not altered.

Scheme 5.8

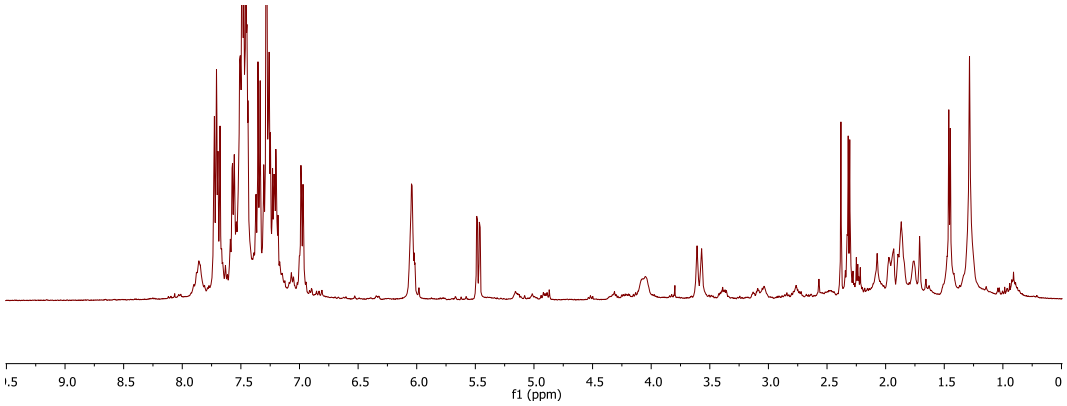


R^1=R^2=H **4.9f**
R^1=F, R^2=H **4.9h**
R^1=H, R^2=OMe **4.9j**

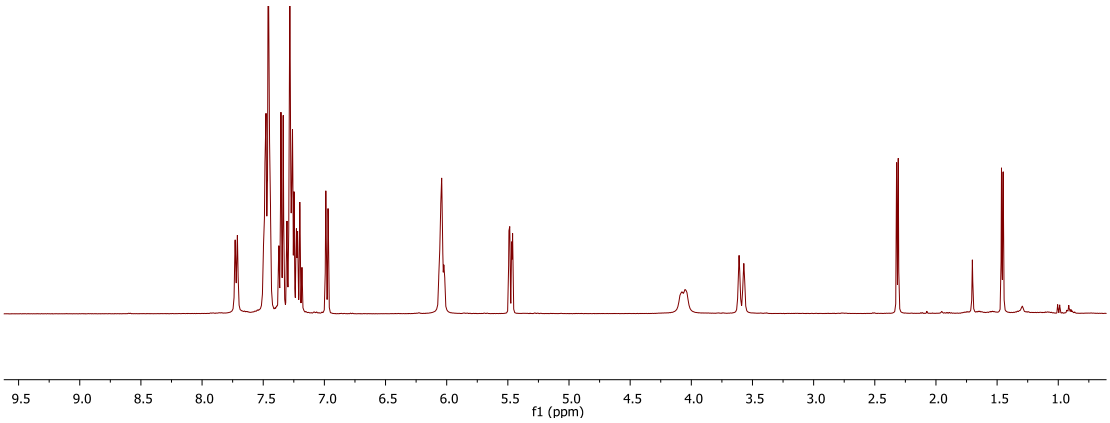
R^1=R^2=H **4.21a** (75%)
R^1=F, R^2=H **4.21c** (69%)
R^1=H, R^2=OMe **4.21e** (70%)

Figure 2

Crude reaction mixture of **4.21f** (Scheme 5.8) ^{1}H NMR in $CDCl_3$

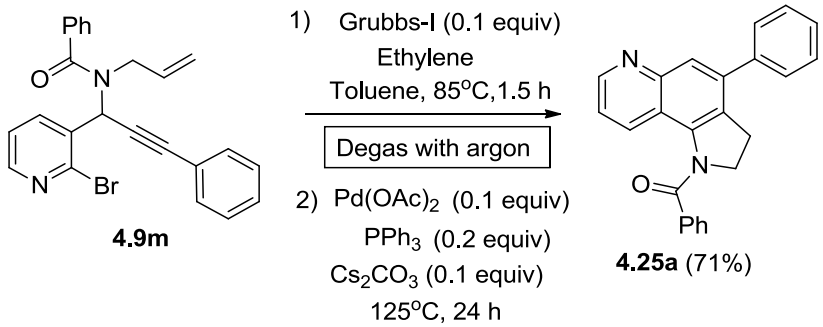


Purified **4.21a** ^{1}H NMR in $CDCl_3$

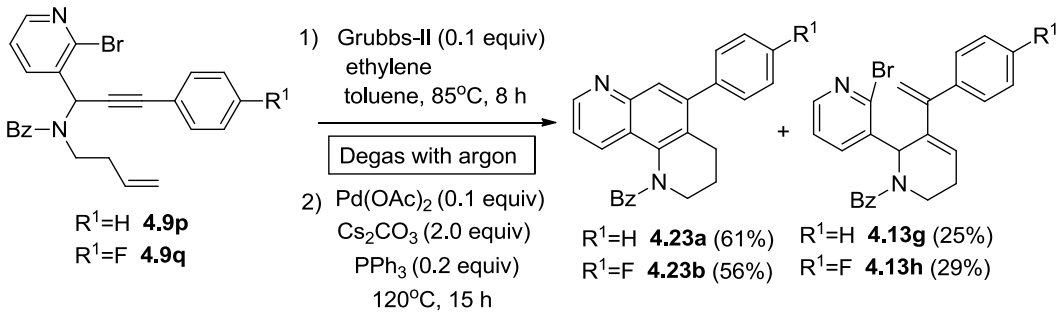


The pyridine-containing enyne **4.9m** furnished pyrroloquinoline **4.25a** (Scheme 5.9). Quinolines **4.23a-b** were also successfully synthesized for their respective enynes **4.9p-q**. However they were accompanied by residual dienes **4.13g-h** formed by the metathesis reaction (Scheme 5.10). The crude mixtures of **4.23** and **4.13** were easily separated by flash chromatography over silica, delivering pure quinolines. Table 1 shows percent increase in the yield via one-pot operation in comparision with the stepwise protocol. The improved yields via one-pot operation highlights the isolation loss of dienes on silica column during the stepwise protocol.

Scheme 5.9



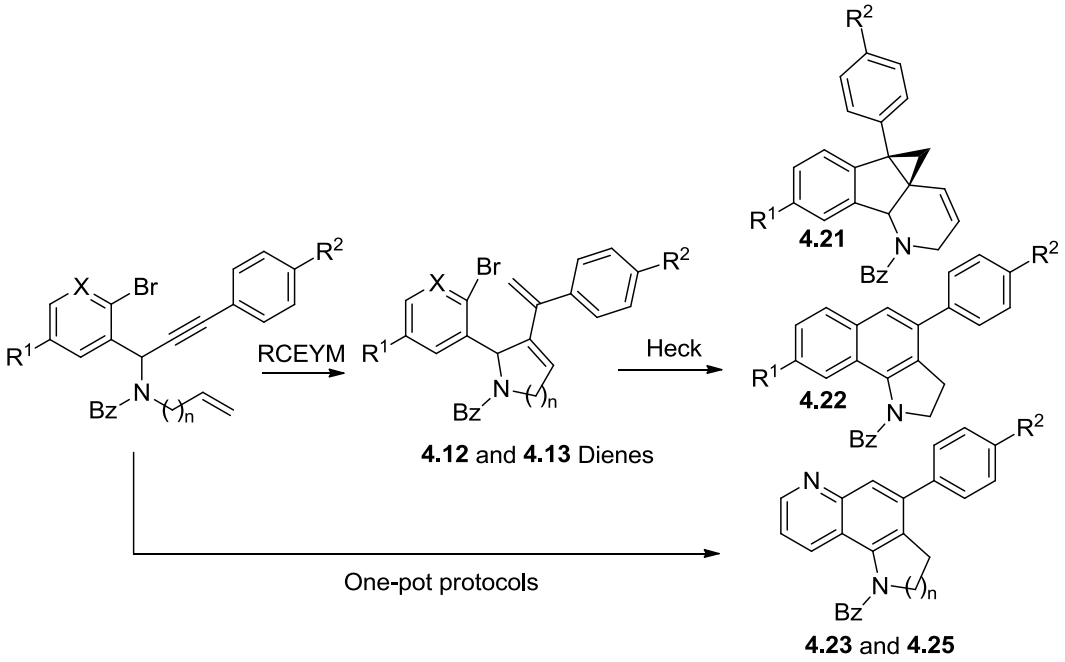
Scheme 5.10



The improvement in the yields of phenanthrolines **4.23a-b** in the one-pot process despite the presence of unreacted dienes **4.13g-h** is notable (Table 1). The involvement of the proposed N−Pd chelation interactions as well as interferences of the metathesis catalytic system with the Pd-catalyst could be the reasons for incomplete conversion. The enynes **4.9p-q** furnishing phenanthrolines **4.23a-b** proved to be challenging substrates for the one-pot protocol. Additional optimization of the Heck reaction conditions for these series may be needed to finetune this protocol for the preparation of phenanthrolines.

The yields of the products from both the two-step sequence and the one-pot protocol are provided in Table 1. The yields of heterocycles **4.21**, **4.22**, **4.23**, and **4.25** obtained via the one-pot protocol (56−75% calculated per the respective enynes) represent 2−22% improvement in comparison to the yields of respective heterocycles achieved via the two-step process.

Table 1



Ent.	n	X	R^1	R^2	% yield Dienes	% yield of Heck rxn. from dienes (stepwise)	% yield of Heck rxn. from enyne (one-pot)	%yield increase in one-pot[a]
1	1	CH	H	H	**4.12a** (93)	**4.22a** (71)	**4.22a** (69)	+3
2	1	CH	F	H	**4.12c** (72)	**4.22c** (65)	**4.22c** (61)	+14
3	1	CH	H	OMe	**4.12e** (63)	**4.22e** (66)	**4.22e** (64)	+22
4	2	CH	H	H	**4.13a** (92)	**4.21a** (80)	**4.21a** (75)	+2
5	2	CH	F	H	**4.13c** (88)	**4.21c** (71)	**4.21c** (69)	+7
6	2	CH	H	OMe	**4.13e** (80)	**4.21e** (80)	**4.21e** (70)	+6
7	1	N	H	H	**4.12g** (69)	**4.25a** (77)	**4.25a** (71)	+18
8	2	N	H	H	**4.13g** (69)	**4.23a** (65)	**4.23a** (61)	+17
9	2	N	H	F	**4.13h** (62)	**4.23b** (61)	**4.23b** (56)	+18

[a]Calcutated as the % yield (column 8) −[% yield (column 7) × % yield (column 6)/100]

Elimination of the material loss during the chromatographic purification of dienes **4.12** and **4.13** appears to be largely responsible for the success of the one-pot protocol for the preparation of heterocycles. Moreover the one-pot protocol provided more economical syntheses by avoiding the expense of time, silica, and solvents involved in chromatographic purification of the RCM products.

5.3 **Conclusions**:

A sequential one-pot protocol for the enyne metathesis and Heck cyclization described in the previous chapter was designed.[177] We believe this is the first ever report on sequential one-pot enyne-RCM/Heck reaction. The analogs synthesized via one-pot protocol showed improved percentage yield (2-22%) when compared to the yields obtained via stepwise protocol. Realizing the Heck reaction in toluene (DMF in stepwise route) was the key for the success. Additional optimization may be needed to finetune this protocol specifically for the preparation of 1,7-tetrahydro phenanthrolines.

Overall Conclusions

Efficient transformation of readily available building blocks into drug-like molecules is the need of the hour. We have demonstrated that sequencing MCRs with transition metal catalyzed annulation reactions is a useful tool for rapid generation of medicinally relevant heterocycles. Treatment of the homologous and isosteric analogs under the same reaction conditions afforded products via different reaction pathways, thus creating a rediodivergent sequence. Moreover designing one-pot protocols for these sequences provides routes for efficient and economical syntheses which would be interesting to medicinal chemists and for the overall profitable pharmaceutical developments

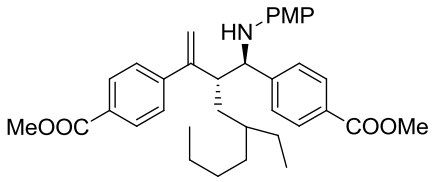
Chapter Six

Experimental

General Experimental

Unless otherwise indicated, all NMR data were collected at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (δ 7.26 ppm for ^1H and 77.00 ppm for ^{13}C). The ^1H NMR and ^{13}C NMR were performed on a 400 MHz and 125 MHz instrument respectively, unless otherwise mentioned. IR spectras were measured as thin films on salt (NaCl) plates. Melting points are uncorrected and were taken in open capillary tubes. MS were measured under electrospray ionization (ES) or fast atom bombardment (FAB) conditions. Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 250 mm thickness, with fluorescent indicator (F-254) or stained with aqueous $KMnO_4$ solution. Column chromatography was performed with 32-63 mm silica gel (Sorbent) or with 150 mesh 58Å pore size basic alumina. Where appropriate neat liquid reagents were added via microliter syringes. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Methylene chloride and toluene were distilled over CaH_2 and sodium metal respectively. DMF and ACN were kept over 3Å (8-12 mesh) molecular sieves under an atmosphere of dry argon; other solvents were used as received. Unless otherwise specified, all reactions were carried out under an atmosphere of dry argon in oven-dried (at least 6h at 140^{o}C) glassware. All imines were prepared according to a modified literature procedure[161] by condensation of a 1 : 1 mixture of aldehyde and amine in methylene chloride in the presence of activated 3Å (8-12 mesh) molecular sieves for 24 h at rt followed by filtration through celite and removal of solvent under vacuum to afford pure imines that were used immediately. The 1-

amino-3-butenes **3.6** and **3.7**[127] and alcohol **3.34a-d**[128] were prepared according to literature protocols. Grubbs I and Grubbs II catalysts were purchased from commercial supplier and used as such. Other materials were used as received from commercial suppliers.



(±)-(2*R*,3*R*)-Ethyl-3-(1-hexyl)-4-(phenyl)-2-(*N*-*p*-methoxyphenylamino)-4-pentenoate (3.8).

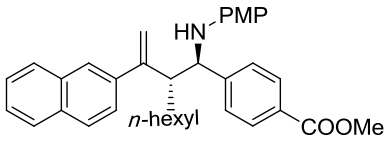
Following the published method,[127] amine **3.8** (0.170 g, 51%) was obtained as a mixture of inseparable diastereomers (9 : 1) as a yellow oil: R_f = 0.58 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 0.1H), 5.39 (s, 0.9H), 5.22 (s, 0.9H), 5.21 (s, 0.1H), 3.87-3.79 (m, 1H), 3.74 (s, 3H), 3.77-3.67 (m, 1H), 3.15 (quintet, *J* = 6.4 Hz, 0.9H), 3.08 (quintet, *J* = 4.4 Hz, 0.1H), 1.75-1.60 (m, 2H), 1.55-1.45 (m, 1H), 1.45-1.20 (m, 10H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, (14.1), 22.6 (27.1), 27.3, 29.4, (29.39) (30.4), 31.0, (31.6), 31.7, (47.0), 47.3, 55.7, 60.6, 60.7, (60.8), (62.3), (114.6), 114.7 (2C), 115.3 (2C), (115.5), 116.0, (126.8), 127.2 (2C), 127.4, 128.1 (2C), (128.3),

141.2, (141.3), 142.4, 148.1, (148.4), 152.6, (152.7), 173.3 signals for the minor diastereomer are given in parentheses.

IR (cm^{-1}) 3373, 1731, 1512; HRMS (ES^+): calcd for $C_{26}H_{36}NO_3$ $(M+H)^+$ 410.2695, found 410.2685.



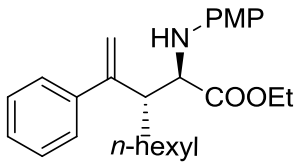
(±)-(1*R*,2*R*)-1-(*N*-*p*-methoxyphenylamino)-1-(*p*-methoxycarbonylphenyl)-2-(1-hexyl)-3-(*2*-naphthyl)-3-butene (3.9).

Following the published method,[127] amine **3.9** (0.540 g, 60%) was obtained as a colorless oil: R_f = 0.25 (EtOAc/Hexane 1 : 9).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.81 (t, *J* = 6.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.72 (t, *J* = 5.0 Hz, 1H), 7.65 (s, 1H), 7.40-7.38 (m, 2H), 7.36-7.31 (m, 3H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.35 (d, *J* = 9.0 Hz, 2H), 5.50 (s, 1H), 5.30 (s, 1H), 4.26 (s br, 1H), 4.18 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 3.66 (s, 3H), 2.90 (td, *J* = 10.0 Hz, 4.0 Hz, 1H), 1.45-1.35 (m, 2H), 1.33-1.25 (m, 2H), 1.22-1.12 (m, 6H), 0.81 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.5, 27.4, 29.2, 30.6, 31.6, 51.9, 53.1, 55.7, 62.3, 114.6 (2C), 114.7 (2C), 117.1, 125.7, 125.9 (2C), 126.2, 127.5, 127.8 (2C), 127.9, 128.1, 128.9, 129.6, 130.2, 132.6, 133.1, 139.3, 141.3, 148.8, 149.6, 152.1, 166.9.

IR (cm^{-1}): 3300, 1720, 1512; HRMS (ES^+): calcd for $C_{35}H_{40}NO_3$ $(M+H)^+$ 522.3008, found 522.2993.



(±)-Ethyl (2*R*,3*R*)-3-hexyl-2-[(4-methoxyphenyl)amino]-4-phenylpent-4-enoate (3.28).

Following the published method,[127] amine **3.28** was obtained as a mixture of inseparable diastereomers (9:1).Yield: 0.170 g (51%); yellow oil. R_f = 0.58 (EtOAc–Hexane, 1:7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 6.75 (d, *J* = 8.8 Hz, 2 H), 6.55 (d, *J* = 8.8 Hz, 2 H), 5.43 (s, 0.1 H), 5.39 (s, 0.9 H), 5.22 (s, 0.9 H), 5.21 (s, 0.1 H), 3.87–3.79 (m, 1 H), 3.74 (s, 3 H), 3.77–3.67 (m, 1 H), 3.15 (quin, *J* = 6.4 Hz, 0.9 H), 3.08 (quin, *J* = 4.4 Hz, 0.1 H), 1.75–1.60 (m, 2 H), 1.55–1.45 (m, 1 H), 1.45–1.20 (m, 10 H), 1.06 (t, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 14.0, (14.1), 22.6, (27.1), 27.3, 29.4, (29.39), (30.4), 31.0, (31.6), 31.7, (47.0), 47.3, 55.7, 60.6, 60.7, (60.8), (62.3), (114.6), 114.7 (2 C), 115.3 (2 C), (115.5), 116.0, (126.8), 127.2 (2 C), 127.4, 128.1 (2 C), (128.3), 141.2, (141.3), 142.4, 148.1, (148.4), 152.6, (152.7), 173.3; signals for the minor diastereomer are given in parentheses.

IR (neat): 3373, 1731, 1512 cm^{-1}; HRMS (ES^+): calcd for $C_{26}H_{36}NO_3$ $(M + H)^+$ 410.2695, found 410.2685.

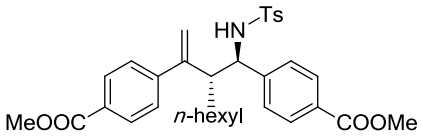
Preparation of *N*-tosylamines 3.14-3.17 and 3.30, via amines 3.10-3.13 and 3.29:

Method A: To solutions of *N*-PMP protected amines **3.6-3.8** and **3.28** (1.0 equiv) in CH_3CN (3-8 mL) was added H_5IO_6 (1.2 equiv) and water (0.2–1.0 mL) was added dropwise, followed by H_2SO_4 (1M aqueous) (0.5-2.0 mL). The mixture was stirred at rt for 24 hours. Water (20 mL) was added, and the mixture was extracted with ether (4 x 20 mL). For small scale preparations, the crude mixture was directly loaded on the silica column for separation eluting with methanol/DCM mixtures to afford deprotected amines **3.10-3.12** and **3.29** as brown to yellow oils that yielded acceptable ^1H and ^{13}C NMR spectra. However, they were not fully characterized.

Method B: To solution of *N*-PMP protected amine **3.9** (1.0 equiv) in CH_3CN (2.0 mL) was added a solution of CAN (1.3 equiv) in water (3.0 mL) at 0 ^oC and the mixture was stirred for 30 minutes at 0 ^oC and 3 hours at rt. Ethyl acetate (30 mL) was added, and the mixture was extracted with 5% aqueous $NaHCO_3$ (30 mL). For methods A and B, organic extracts were dried ($MgSO_4$), and solvents were removed under reduced pressure to afford crude products that were partially purified by flash chromatography over silica eluting with methanol/DCM mixtures to afford amine **3.13** as yellow oil. However, it was not fully characterized and was used as such for further reaction.

General procedure for *N*-tosylation:

Amines **3.10-3.13** and **3.29** (1.0 equiv) were dissolved in THF (5-12 mL), *p*-toluenelsulfonyl chloride (1.6 equiv) and triethylamine (1.1 equiv) were added at 0^{o}C and the mixture was stirred at rt under argon for 18 hours. Water (6-10 mL) was added, and the mixture was extracted with ether (4 x 20 mL). Organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over silica to afford *N*-tosylamines **3.14-3.17** and **3.30** as colorless to yellow oils.



(±)-(1*R*,2*R*)-1-(*N*-tosylamino)-2-hexyl-1-(*p*-methoxycarbonylphenyl)-3-(*p*-methoxycarbonylphenyl)-3-butene (3.14).

Following Method A, amine intermediate **3.10** and following *N*-tosylation protocol *N*-tosylamine **3.14** were isolated.

Analytical data for 3.10:

Yield: 0.216 g (73%); brown oil.

R_f = 0.35 (MeOH–CH_2Cl_2, 1:19). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.0 Hz, 2 H), 7.97 (d, *J* = 8.0 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 5.52 (s, 1 H), 5.29 (s, 1 H), 4.00 (d, *J* = 9.0 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 2.83–2.72 (m, 1 H), 2.29 (br s, 2 H), 1.34–1.01 (m, 10 H), 0.77 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.5, 27.1, 29.2, 29.7, 31.6, 32.4, 52.1, 52.7, 60.3, 116.2, 126.8 (2 C), 127.5 (2 C), 128.9, 129.2, 129.6 (2 C), 129.7 (2 C), 148.0, 149.6, 150.2, 166.92, 166.98.

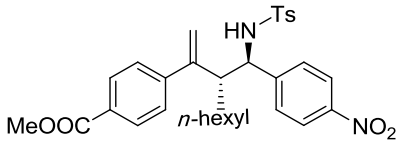
Analytical data for 3.14:

Yield: 0.379 g (64%); yellow oil. R_f = 0.32 (EtOAc/Hexane 1 : 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.61 (d, *J* = 6.5 Hz, 1H), 5.35 (s, 1H), 5.07 (s, 1H), 4.28 (t, *J* = 6.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.18-2.77 (m, 1H), 2.21 (s, 3H), 1.20-1.15 (m, 4H), 1.14-1.09 (m, 2H), 1.05-0.87 (m, 4H), 0.70 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.3, 22.4, 26.8, 29.1, 30.7, 31.5, 50.7, 52.0, 52.1, 60.6, 118.2, 126.7 (2C), 127.0 (2C), 127.5 (2C), 128.9, 129.0, 129.1 (2C), 129.2 (2C), 129.6 (2C), 137.1, 143.1, 144.3, 146.4, 147.2, 166.7, 166.8.

IR (cm^{-1}) 3276, 1722; HRMS (ES^+): calcd for $C_{33}H_{39}NO_6SNa$ $(M+Na)^+$ 600.2396, found 600.2380.



(±)-(1*R*,2*R*)-1-(*N*-tosylamino)-1-(*p*-nitrophenyl)-2-(1-hexyl)-3-(*p*-methoxycarbonylphenyl)-3-butene (3.15).

Following method A amine intermediate **3.11** and following *N*-tosylation protocol *N*-tosylamine **3.15** were isolated

Analytical data for 3.11:

Yield: 0.212 g (72%); brown oil.

R_f = 0.40 (MeOH–CH_2Cl_2, 1:19); ^{1}H NMR (500 MHz, CDCl3): δ = 8.15 (d, *J* = 8.5 Hz, 2 H), 7.99 (d, *J* = 8.5 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 5.54 (s, 1 H), 5.29 (s, 1 H), 4.08 (d, *J* = 8.5 Hz, 1 H), 3.92 (s, 3 H), 2.79 (td, *J* = 9.0, 3.0 Hz, 1 H), 1.90–1.69 (m, 2 H), 1.34–1.05 (m, 10 H), 0.78 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.5, 27.1, 29.2, 31.6, 32.2, 52.2, 52.6, 59.9, 116.5, 123.5 (2 C), 126.8 (2 C), 128.4 (2 C), 129.1, 129.7 (2 C), 147.2, 147.7, 149.6, 151.8, 166.8.

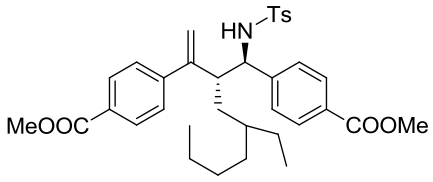
Analytical data for 3.15:

Yield: 0.280 g (62%); yellow oil. R_f = 0.30 (EtOAc/Hexane 1 : 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 4.5 Hz, 2H), 7.17 (d, *J* = 4.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.51 (s, 1H), 5.19 (s, 1H), 5.09 (d, *J* = 5.5 Hz, 1H), 4.37 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H), 3.92 (s, 3H), 2.85-2.81 (m, 1H), 2.34 (s, 3H), 1.32-1.04 (m, 10H), 0.80 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.4, 22.5, 27.0, 29.0, 30.8, 31.5, 51.2, 52.2, 60.0 118.9, 123.2 (2C), 126.6 (2C), 127.1 (2C), 128.4 (2C), 129.4 (2C), 129.5, 129.8 (2C), 136.8, 143.8, 145.6, 146.9, 147.0, 147.1, 166.6.

IR (cm^{-1}) 3276, 1720; HRMS (ES^+): calcd for $C_{31}H_{36}N_2O_6SNa$ $(M+Na)^+$ 587.2192, found 587.2180.



(±)-(1*R*,2*R*)-2-(2-Ethylhexyl)-1,3-bis[4-(methoxycarbonyl)phenyl]-1-(tosylamino) but-3-ene (3.16).

Following Method A, the amine intermediate **3.12** and following *N*-tosylation protocol the *N*-tosylamine **3.16** were isolated.

Analytical data for 3.12:

Yield: 0.224 g (76%); brown oil. R_f = 0.30 (MeOH–CH_2Cl_2, 1:19).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (t, *J* = 8.0 Hz, 4 H), 7.52 (dd, *J* = 8.5, 2.0 Hz, 2 H), 7.45 (dd, *J* = 8.0, 1.5 Hz, 2 H), 5.54 (s, 1 H), 5.33 (s, 1 H), 4.00 (d, *J* = 9.0 Hz, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 2.93–2.87 (m, 1 H), 2.06–1.77 (m, 2 H), 1.36–0.94 (m, 9 H), 0.91–0.88 (m, 2 H), 0.80 (t, *J* = 7.5 Hz, 1.5 H), 0.72 (t, *J* = 7.5 Hz, 1.5 H), 0.65 (t, *J* = 7.5 Hz, 1.5 H), 0.46 (t, *J* = 7. Hz, 1.5 H); two diastereomers arise from the stereocenter in the branched alkyl substituent.

Analytical data for 3.16:

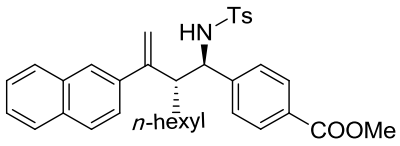
Yield: 0.270 g (72%); pale-yellow oil. R_f = 0.45 (EtOAc/Hexane, 1:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 8.5, 1.5 Hz, 2 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 7.37(d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H),

7.02 (d, *J* = 8.0 Hz, 2 H), 5.43 (s, 1 H), 5.16 (s, 1 H), 5.03 (t, *J* = 4.5 Hz, 1 H), 4.29 (quin, *J* = 3.5 Hz, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 2.85 (td, *J* = 11.3, 3.0 Hz, 1H), 2.32 (s, 3 H), 1.35–1.23 (m, 2 H), 1.21–0.82 (m, 9 H), 0.79 (t, *J* = 7.5 Hz, 1.5 H), 0.75 (t, *J* = 7.5 Hz, 1.5 H), 0.63 (t, *J* = 6.0 Hz, 1.5 H), 0.51 (t, *J* = 7.5 Hz, 1.5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.4 (10.8), 14.0, 21.3, 22.8 (22.9), 24.4, 26.3, 27.6 (28.7), 31.5 (33.0), 34.7, 35.3 (35.7), 49.0 (49.1), 52.1 (52.2), 60.8 (60.9), 119.10 (119.11), 126.8 (2 C) (126.9), 127.1 (2 C), 127.6 (2 C) (127.7), 129.1 (2 C) (129.2), 129.31 (2 C) (129.32), 129.37, 129.61 (129.65), 129.68 (2 C) (129.69), 136.94 (136.96), 143.2, 144.4 (144.5), 145.8 (145.9), 147.9, (166.63) 166.65, 166.7. Signals for the minor diastereomer arising from the stereocenter in the side chain are given in parentheses.

IR (neat): 3278, 1722 cm^{-1}; HRMS (ES^+): calcd for $C_{35}H_{43}NO_6SNa$ $(M+Na)^+$ 628.2709, found 628.2701.



(±)-(1*R*,2*R*)-1-(*N*-tosylamino)-1-(*p*-methoxycarbonylphenyl)-2-(1-hexyl)-3-(2-napththyl)-3-butene (3.17).

Following method B amine intermediate **3.13** was obtained and was not characterized; following *N*-tosylation protocol *N*-tosylamine **3.17** was isolated.

Analytical data for 3.14:

Yield: 0.043 g (48%); yellow oil.

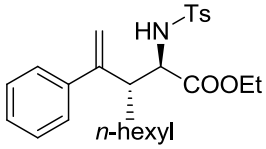
Analytical data for 3.17:

Yield: 0.213 g (65%); yellow oil. R_f = 0.33 (EtOAc/Hexane 1 : 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.74 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 5 Hz, 1H), 7.60 (d, *J* = 1.0 Hz, 1H), 7.48 (t, *J* = 1.5 Hz, 1H), 7.39 (t, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.37-7.30 (m, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 7.5 Hz, 2H), 5.54 (s, 1H), 5.18 (s, 1H), 5.09 (d, *J* = 5.0 Hz, 1H), 4.37 (dd, *J* = 8.5 Hz, 5.0 Hz, 1H), 3.86 (s, 3H), 2.93 (td, *J* = 8.5 Hz, 4.0 Hz, 1H), 2.27 (s, 3H), 1.36-1.06 (m, 10H), 0.78 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.1, 21.8, 27.1, 29.1, 30.8, 31.5, 51.5, 52.0, 60.8, 117.5, 123.6, 125.0, 125.5, 126.1, 126.3, 127.1, 127.5, 127.7, 128.1, 128.2, 128.5, 129.1 (2C), 129.2 (2C), 129.8, 132.7, 133.1, 136.9, 138.6, 143.1, 144.6, 148.0, 166.7.

IR (cm^{-1}) 3200, 1722; HRMS (ES^+): calcd for $C_{35}H_{39}NO_4SNa$ ($M+Na^+$) 592.2498, found 592.2480.



(±)-(2*R*,3*R*)-Ethyl-3-(1-hexyl)-4-(phenyl)-2-(*N*-tosylamine)-4-pentenoate (3.30). Following Method A, the amine intermediate **3.29** was obtained as a mixture of inseparable diastereomers (9:1), and following *N*-tosylation protocol N-tosylamine 6e was isolated as a single diastereomer.

Analytical data for 3.29:

Yield: 0.150 g (60%); brown oil. R_f = 0.25 (EtOAc/Hexane, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.23 (m, 5 H), 5.45 (s, 0.1H), 5.40 (s, 0.9 H), 5.17 (s, 0.9 H), 5.14 (s, 0.1 H), 3.83–3.75 (m, 1 H), 3.53 (d, *J* = 5.2 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.15 (quin, *J* = 5.6 Hz, 1 H), 2.36 (br s, 2 H), 1.75–1.60 (m, 2 H), 1.55–1.10 (m, 8 H), 1.04 (t, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

Analytical data for 3.30:

Yield: 0.118 g (55%); yellow oil. R_f = 0.7 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.26-7.21 (m, 7H), 5.40 (s, 1H), 5.20 (s, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.97 (dd, *J* = 4.0 Hz, 10.4 Hz, 1H), 3.37-3.27 (m, 1 H), 3.21-3.15 (m, 1H), 3.14-3.06 (m, 1H), 2.39 (s, 3H), 1.78-1.66 (m, 2H), 1.48-1.23 (m, 8 H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.77 (t, *J* = 7.2 Hz, 3H).

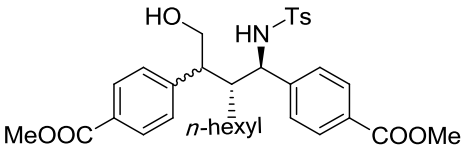
^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 14.1, 21.4, 22.6, 27.1, 29.3, 31.6, 31.7, 45.8, 57.5, 61.1, 116.4, 126.8 (2C), 127.2 (2C), 127.5, 128.1 (2C), 129.4 (2C), 136.8, 142.4, 143.4, 146.6, 170.2.

IR (cm^{-1}) 3276, 1737, 1598; HRMS (ES^+): calcd for $C_{26}H_{35}NO_4SNa$ $(M+Na)^+$ 480.2185, found 480.2169.

Preparation of aminoalcohols 3.18-3.21 and diols 3.35a-d:

To a solution of *N*-tosylamines **3.14-3.17** or alcohols **3.35a-d** (1.0 equiv) in THF (5-10 mL) at 0 ^oC was added BH_3.THF complex (1M in THF, 5.0 equiv) and the solution was stirred at rt under argon for 24 hours or only 4 hours for alcohols **3.35**. An aqueous solution of NaOH (3M, 9.0 equiv) was added at 0 ^oC, followed by H_2O_2

(30% aqueous solution, 9.0 equiv) and the mixture was stirred for 30 minutes at 0 ^{o}C and 2 hours at rt. Water (20 mL) was added, and the mixture was extracted (EtOAc, 4 x 20 mL). Organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over silica to afford aminoalcohols **3.18-3.21** or diol **3.35**.



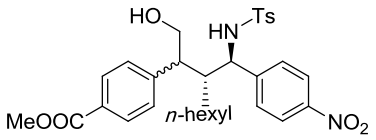
(±)-(1*R*,2*R*,3*S*)-1-(*N*-tosylamino)-2-hexyl-1-(*p*-methoxycarbonylphenyl)-3-(*p*-methoxycarbonylphenyl)-4-hydroxy-1-butane (3.18).

Aminoalcohol **3.18** (0.048 g, 65%) was obtained as a colorless oil: R_f = 0.45 (EtOAc/Hexane 1 : 1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.20 (d, *J* = 8.5 Hz, 1H), 4.44 (t, *J* = 8.0 Hz, 1H), 3.93-3.85 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.79 (dd, *J* = 10.5 Hz, 8.0 Hz, 1H), 3.32 (q, *J* = 6.0 Hz, 1H), 2.52 (s br, 1H), 2.27 (s, 3H), 2.25-2.20 (m, 1H), 1.10-1.10 (m, 3H), 0.92-0.75 (m, 7H), 0.72 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.3, 22.4, 27.7, 28.3, 29.2, 31.3, 45.6, 48.0, 52.1, 52.2, 59.7, 64.2, 126.8 (2C), 127.3 (2C), 128.7, 128.8, 128.9 (2C), 129.2 (2C), 129.4 (2C), 129.8 (2C), 137.5, 143.1, 145.4, 145.9, 166.7, 167.0.

IR (cm^{-1}) 3500, 3271, 1722; HRMS (ES^+): calcd for $C_{33}H_{41}NO_7SNa$ $(M+Na)^+$ 618.2501, found 618.2510.



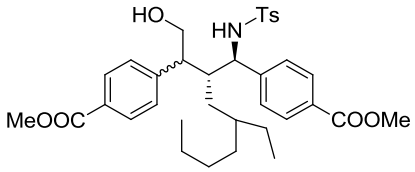
(±)-(1*R*,2*R*,3*S*)-1-(*N*-tosylamino)-1-(*p*-nitrophenyl)-2-hexyl-3-(*p*-methoxycarbonylphenyl)-4-hydroxy-1-butane (3.19).

Aminoalcohol **3.19** (0.140 g, 61%) was obtained as a colorless oil: R_f = 0.30 (EtOAc/Hexane 1 : 1).

^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.51 (d, *J* = 8.5 Hz, 1H), 4.47 (t, *J* = 8.5 Hz, 1H), 3.95-3.89 (m, 1H), 3.91 (s, 3H), 3.82 (dd, *J* = 10.5 Hz, 3.0 Hz, 1H), 3.33 (q, *J* = 5.5 Hz, 1H), 2.78 (s br, 1H), 2.32-2.25 (m, 1H), 2.28 (s, 3H), 1.12-0.99 (m, 3H), 0.90-0.65 (m, 7H), 0.72 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.3, 22.3, 27.7, 28.4, 29.2, 31.3, 45.5, 48.0, 52.2, 59.6, 64.1, 125.9, 126.3, 126.6, 126.8 (2C), 127.1, 127.6, 127.7, 128.5, 128.8, 129.2, 129.4, 132.5, 133.4, 137.7, 137.8, 143.0, 146.0, 166.7.

IR (cm^{-1}) 3492, 3375, 3269, 1720; HRMS (ES^+): calcd for $C_{31}H_{38}N_2O_7SNa$ $(M+Na)^+$ 605.2297, found 605.2310.



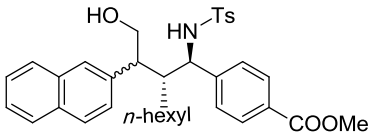
(±)-(1*R*,2*R*,3*S*)-2-(2-Ethylhexyl)-4-hydroxy-1,3-bis[4-(methoxycarbonyl) phenyl]-1-(tosylamino)butane (3.20).

Aminoalcohol **3.20** (0.166 g 66%) was obtained as colorless oil: R_f = 0.41 (EtOAc–Hexane, 3:7).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.5, 7.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.41 (dd, *J* = 8.0, 5.5 Hz, 2 H), 7.25 (dd, *J* = 8.5, 5.0 Hz, 2 H), 7.09 (d, *J* = 8.5 Hz, 2 H), 7.02 (d, *J* = 7.5 Hz, 2 H), 5.62 (t, *J* = 9.5 Hz, 1 H), 4.52 (t, *J* = 6.0 Hz, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.82–3.77 (m, 1 H), 3.75–3.67 (m, 1 H), 3.20 (quin, *J* = 5 Hz, 1 H), 2.35–2.29 (m, 1 H), 2.29 (s, 3 H), 1.76 (br s, 1 H), 1.22–0.97 (m, 4 H), 0.94–0.82 (m, 7 H), 0.81 (t, *J* = 6.0 Hz, 1.5 H), 0.77 (t, *J* = 7.5 Hz, 1.5 H), 0.57 (t, *J* = 7.0 Hz, 1.5 H), 0.50 (t, *J* = 7.0 Hz, 1.5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (14.2), 21.1 (21.3), 23.06 (23.09), 24.0 (25.5), 27.7 (28.2), 31.2, 32.5, 32.9 (33.0), 35.9 (36.0), 43.7, 43.8, (48.3) 48.4, 52.1, 59.8 (60.4), 64.0, 126.81 (126.83) (2 C), 127.1 (2 C), 128.81 (128.84), 128.92 (128.95), 129.0, 129.2 (2 C), 129.4 (2 C), 129.8 (2 C), 137.6 (137.7), 143.10 (143.13), 145.7, 145.84, 145.88, 166.65 (166.66), 166.83 (166.86); signals for the minor diastereomer arising from the stereocenter in the side chain are given in parentheses.

IR (neat): 3494, 3272, 1722 cm^{-1}; HRMS (ES^+): calcd for $C_{35}H_{46}NO_7S$ $(M+H)^+$ 624.2995, found 624.3000.

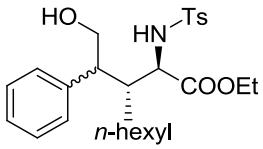


(±)-(1*R*,2*R*,3*S*)-1-(*N*-tosylamino)-1-(*p*-methoxycarbonylphenyl)-2-hexyl-3-(2-napththyl)-4-hydroxy-1-butane (3.21).

Aminoalcohol **3.21** (0.066 g, 56%) was obtained as a pale yellow oil: R_f = 0.25 (EtOAc/Hexane 3 : 7).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.79 (m, 5H), 7.62 (s br, 1H), 7.52-7.47 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.54 (d, *J* = 8.0 Hz, 1H), 4.65 (t, *J* = 6.5 Hz, 1H), 3.91-3.87 (m, 1H), 3.90 (s, 3H), 3.82-3.74 (m, 1H), 3.18 (q, *J* = 5.5 Hz, 1H), 2.35-2.28 (m, 1H), 2.30 (s, 3H), 1.66-1.59 (s br, 1H), 1.14-1.06 (m, 2H), 1.03-0.90 (m, 8H), 0.75 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.4, 22.5, 27.8, 28.5, 29.2, 31.5, 46.3, 48.2, 52.1, 59.3, 64.8, 125.9, 126.4, 126.7, 126.8 (2C), 127.1 (2C), 127.6, 127.8 (2C), 128.6, 128.8, 129.2 (2C), 129.4 (2C), 132.6, 133.4, 137.7, 137.8, 143.0, 146.0, 166.7. IR (cm^{-1}) 3488, 3365, 3272, 1722; HRMS (ES^+) calcd for $C_{35}H_{41}NO_5SNa$ $(M+Na)^+$ 610.2603, found 610.2570.



(±)-(2*R*,3*R*,4*S*)-Ethyl-3-(1-hexyl)-4-(phenyl)-2-(*N*-tosylamino)-5-hydroxy-pentanoate (3.31).

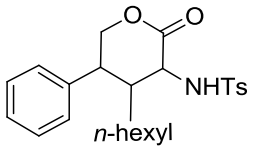
To a solution of *N*-tosylamine **3.30** (0.105 g, 0.23 mmol, 1 equiv) in THF (5 mL) at 0 ^{o}C was added BH_3·THF (1M solution, 0.75 mL, 1.38 mmol, 6 equiv) dropwise. The mixture was stirred for 1 h at 0^{o}C, and the stirring was continued for 10 h at rt. Water (2 mL) was added, followed by and $NaBO_3 \cdot 4H_2O$ (0.531 g, 3.45 mmol, 15 equiv) and the mixture was stirred for 1h at rt. Purification procedure described for alcohols **3.18**-**3.21** above was followed to afford alcohol **7d** (0.070 g, 65%) as a colorless oil and lactone **3.32** (0.027 g, 25%).

Aminoalcohol 3.31: R_f = 0.25 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.37-7.25 (m, 5H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.48 (d, *J* = 9.6 Hz, 1H), 4.18 (dd, *J* = 3.2 Hz, 10.0 Hz, 1H), 4.01 (dq, *J* = 7.2 Hz, 2.0 Hz, 2H), 3.76 (t, *J* = 5.6 Hz, 2H), 2.87 (q, *J* = 6.4 Hz, 1H), 2.43 (s, 3H), 2.38-2.30 (m, 1H), 1.75 (t, *J* = 5.2 Hz, 1H), 1.35-0.97 (m, 10H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 21.5, 22.5, 27.3, 28.9, 29.1, 31.5, 43.7, 49.4, 56.7, 61.7, 65.3, 127.2 (2C), 127.3, 128.5 (2C), 128.8 (2C), 129.5 (2C), 137.2, 140.7, 143.4, 172.2.

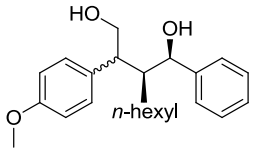
IR (cm^{-1}) 3575, 3200, 1745; HRMS (ES^{+}): calcd for $C_{26}H_{37}NO_5SNa$ $(M+Na)^{+}$ 498.2290, found 498.2286.



Lactone 3.32: R_f = 0.55 (EtOAc/Hexane 1 : 7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.42-7.26 (m, 7H), 5.57 (d, *J* = 4.8 Hz, 1H), 4.44 (dd, *J* = 5.2 Hz, 6.8 Hz, 1H), 4.43 (dd, *J* = 6.8 Hz, 12.0 Hz, 1H), 4.20 (t, *J* = 11.6 Hz, 1H), 3.13-3.08 (m, 1H), 2.69-2.62 (m, 1H), 2.43 (s, 3H), 1.78-1.68 (m, 1H), 1.34-1.07 (m, 7H), 1.05-0.95 (m, 2H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.5, 22.5, 26.0, 29.0, 30.5, 31.5, 42.6, 44.5, 53.9, 70.8, 127.0 (2C), 127.4 (2C), 127.7, 129.2 (2C), 129.9 (2C), 136.3, 139.7, 144.0, 170.9.

IR (neat, cm^{-1}) 3285, 1755; HRMS (ES^+): calcd for $C_{24}H_{31}NO_4SNa$ $(M+Na)^+$ 452.1872, found 452.1869.



(±)-(1*R*,2*S*,3*R*)-1-phenyl-2-(1-hexyl)-3-(*p*-methoxyphenyl)-1,4-dihydroxybutane (3.35a).

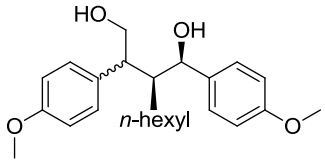
Diol **3.35a** (0.143 g, 85%) was obtained as a heavy oil as a mixture (3 : 1) of inseparable diastereomers: R_f = 0.58 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 7H), 6.95 (d, *J* = 8.4 Hz, 0.5H), 6.90 (d, *J* = 8.4 Hz, 1.5H), 5.05 (s, 0.75H), 4.67 (s, 0.25H), 4.09 (d, *J* = 4.8 Hz, 1.5H), 4.03-3.96

(br, 0.25H), 3.88 (t, *J* = 9.2 Hz, 0.25H), 3.83 (s, 3H), 3.13-3.07 (m, 0.25H), 3.49 (q, *J* = 6.0 Hz, 0.75H), 2.70-2.57 (m, 1H), 2.47-2.33 (m, 1H), 2.05-2.00 (m, 0.75H), 1.96-1.87 (m, 0.25H), 1.41-1.23 (m, 2H), 1.20-0.86 (m, 8H), 0.79 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, (22.5), (25.4), 25.7, 28.1, (28.9), 29.3, (29.5), 31.4, 47.9, (48.1), 49.4, (50.1), 55.2, (55.3), 64.1, (65.0), 72.8, (73.8), 113.9 (2C), (114.4), (125.3), 125.6 (2C), (126.6), 126.8, (128.0), 128.1 (2C), (129.41), 129.45 (2C), (133.6), 134.5, 143.9, (144.0), 158.2, (158.5) signals for the minor diastereomer are given in parentheses.

IR (cm^{-1}) 3373, 1724, 1606; HRMS (FAB): calcd for $C_{23}H_{32}O_3$ $(M)^+$ 356.2351, found 356.2347.



(±)-(1*R*,2*S*,3*R*)-1-(*p*-methoxyphenyl)-2-(1-hexyl)-3-(*p*-methoxyphenyl)-1,4-dihydroxybutane (3.35b).

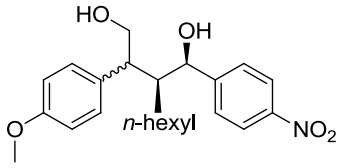
Diol **3.35b** (0.09 g, 92%) was obtained as a heavy oil as a mixture (3 : 1) of inseparable diastereomers: R_f = 0.45 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.19-7.16 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 0.5H), 6.90-6.84 (m, 3.5H), 4.98 (d, *J* = 2.0 Hz, 0.75H), 4.63 (d, *J* = 2.4 Hz, 0.25H), 4.06 (d, *J* = 5.2 Hz, 1.5H), 3.98 (dd, *J* = 10.8 Hz, *J* = 5.2 Hz, 0.25H), 3.86 (dd, *J* = 10.8 Hz, *J* = 8.4 Hz, 0.25H), 3.83 (s, 3H), 3.81 (s, 3H), 3.10-3.05 (m, 0.25H),

3.02 (q, *J* = 6.8 Hz, 0.75H), 2.33 (br, 2H), 2.02-1.96 (m, 0.75H), 1.90-1.83 (m, 0.25H), 1.40-1.24 (m, 2H), 1.21-0.98 (m, 7H), 0.96-0.87 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (14.02), 14.05, 22.51, (22.57), (25.4), 25.9, (28.0), 28.1, (29.0), 29.4, 31.51, (31.58), 47.8, (48.3), 49.3, (50.0), 55.2, (55.6), 64.1, (65.0), 72.6, (73.6), (74.64), 75.4, (113.7) , 113.8 (2C), 114.0 (2C), (114.3), (126.4), 126.7 (2C), (127.6), 128.0 (2C), (132.9), (133.7), 134.0, 134.3, 158.2, (158.3), 158.4, (158.5), signals for the minor diastereomer are given in parentheses.

IR (cm^{-1}) 3650, 1512, 1247; HRMS (ES^+): calcd for $C_{24}H_{34}O_4Na$ $(M+Na)^+$ 409.2355, found 409.2384.



(±)-(1*R*,2*S*,3*R*)-1-(*p*-nitrophenyl)-2-(1-hexyl)-3-(*p*-methoxyphenyl)-1,4-dihydroxybutane (3.35c).

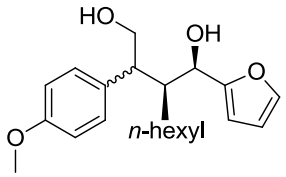
Diol **3.35c** (0.065 g, 62%) was obtained as a heavy oil as a mixture (3 : 1) of inseparable diastereomers: R_f = 0.38 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 0.5H), 6.87 (d, *J* = 8.8 Hz, 1.5H), 5.14 (s, 0.75H), 4.77 (s, 0.25H), 4.13 (m, 1.5H), 4.03 (dd, *J* = 10.8 Hz, *J* = 5.6 Hz, 0.25H), 3.91 (dd, *J* = 10.4 Hz, *J* = 7.6 Hz, 0.25H) 3.83 (s, 3H), 3.14-3.06 (m, 1H), 2.51 (br,

2H), 2.09-2.01 (m, 0.75H), 1.99-1.94 (m, 0.25H), 1.31-1.24 (m, 2H), 1.17-0.92 (m, 7H), 0.85-0.74 (m, 1H), 0.78 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.4, (22.5), (25.3), 25.7, 27.9, (28.8), 29.2, (29.4), 31.7, 47.6, (48.1), (50.0), 50.2, 55.2, (55.3), 64.0, (64.8), 71.7, (73.4), 114.1 (2C), (114.6), 123.2 (2C), (123.3), (126.3), 126.5 (2C), 129.3 (2C), (133.1), 134.2, 146.7, 152.0, 158.4, (158.8), signals for the minor diastereomer are given in parentheses.

IR (cm^{-1}) 3440, 1637, 1550, 1250; HRMS (FAB): calcd for $C_{23}H_{31}NO_5$ $(M)^+$ 401.2202, found 401.2197.



(±)-(1*R*,2*S*,3*R*)-1-furyl-2-(1-hexyl)-3-(*p*-methoxyphenyl)-1,4-dihydroxybutane (3.35d).

Diol **3.35d** (0.082 g, 68%) was obtained as a heavy oil as a mixture (3 : 1) of inseparable diastereomers: R_f = 0.5 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.6 Hz, *J* = 0.8 Hz, 0.75H), 7.33 (dd, *J* = 2.0 Hz, *J* = 0.8 Hz, 0.25H), 7.26 (d, *J* = 1.6 Hz, 0.5H), 7.22 (d, *J* = 8.8 Hz, 1.5H), 6.92 (d, *J* = 8.8 Hz, 0.5H), 6.88 (d, *J* = 8.4 Hz, 1.5H), 6.37 (dd, *J* = 3.2 Hz, *J* = 2.0 Hz, 0.75H), 6.33 (dd, *J* = 3.2 Hz, *J* = 2.0 Hz, 0.25H), 6.28 (dt, *J* = 3.2 Hz, *J* = 0.8 Hz, 0.75H), 6.20 (dt, *J* = 3.2 Hz, *J* = 0.8 Hz, 0.25H), 5.03(d, *J* = 2.4 Hz, 0.75H), 4.63 (d, *J*

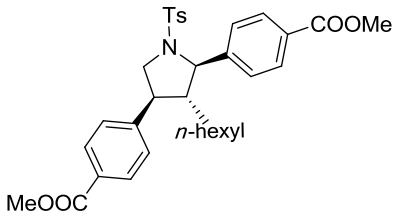
= 1.6 Hz, 0.25H), 4.07-3.94 (m, 1.75H), 3.88-3.83 (m, 0.25H), 3.82 (s, 3H), 3.07-3.02 (m, 0.25H), 2.94-2.89 (m, 0.75H), 2.36 (br, 2H), 2.27-2.21 (m, 0.75H), 2.13-2.08 (m, 0.25H), 1.40-1.03 (m, 10H), 0.83 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.02, (14.06), 22.52, (22.53), 27.8, (27.94), (27.97), 28.0, (29.31), 29.33, 31.48, (31.59), (47.7), (48.2), 49.7, 51.2, (55.24), 55.28, (68.9), (74.2), 74.9, 75.2, (107.7), 108.1, 109.9, (110.1), (113.7), 114.0 (2C), 128.8 (2C), (129.3), 132.3, (132.7), 142.0, (142.5), 154.5, (154.6), (158.2), 158.4, signals for the minor diastereomer are given in parentheses.

IR (cm^{-1}) 3700, 1610, 1514, 1249; HRMS (FAB): calcd for $C_{21}H_{30}NO_4$ $(M)^+$ 346.2144, found 346.2170.

Preparation of pyrrolidines 3.22-3.25, 3.33 and tetrahydrofuran 3.36a-d:

To a solution of aminoalcohols **3.18-3.21, 3.30** or diols **3.35a-d** (1.0 equiv) in DCM (2-5 mL) at 0^{o}C was added pyridine (12 equiv) and tosylchloride (3.0 equiv). The solution was stirred for 30 minutes at 0^{o}C and 24 h at rt. Cold water (5 mL) was added, and the mixture was extracted with DCM (4 x 20 mL). Combined organic layers were dried ($MgSO_4$), and solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over silica to afford pyrrolidines **3.22-3.25** and tetrahydrofuran **3.36a-d**.



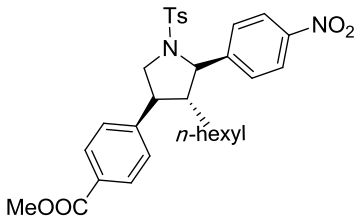
(±)-(2*R*,3*R*,4*S*)-*N*-toluenesulfonyl-3-(1-hexyl)-2-(*p*-methoxycarbonylphenyl)-4-(*p*-methoxycarbonylphenyl)-pyrrolidine (3.21).

Pyrrolidine **3.21** (0.037 g, 66%) was obtained as a white solid: mp 169-171 ^{o}C; R_f = 0.8 (EtOAc/Hexane 3 : 7).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 6.5 Hz, 1.5 Hz, 4H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.24 (dd, *J* = 8.0 Hz, 2.0, 4H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.10 (dd, *J* = 11.0 Hz, 8.0 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.56 (t, *J* = 11.5 Hz, 1H), 2.79 (hex, *J* = 7.5 Hz, 1H), 2.41 (s, 3H), 2.35-2.28 (m, 1H), 1.30-1.21 (m, 2H), 1.08-1.02 (m, 2H), 0.95-0.88 (m, 4H), 0.84-0.77 (m, 2H), 0.73 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.5, 22.3, 26.2, 29.1, 30.2, 31.3, 49.9, 52.1, 52.2, 55.9, 56.3, 69.1, 127.3 (2C), 127.4 (2C), 127.7 (2C), 129.3, 129.4, 129.6 (2C), 129.8 (2C), 130.1 (2C), 135.5, 143.6, 144.2, 147.1, 166.7, 166.8.

IR (cm^{-1}) 1722; HRMS (ES^{+}): calcd for $C_{33}H_{39}NO_6SNa$ $(M+Na)^{+}$ 600.2396, found 600.2372.



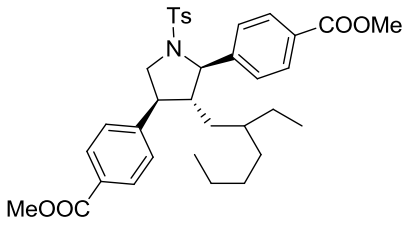
(±)-(2*R*,3*R*,4*S*)-*N*-toluenesulfonyl-3-(1-hexyl)-4-(*p*-methoxycarbonylphenyl)-2-(*p*-nitrophenyl)-pyrrolidine (3.22).

Pyrrolidine **3.22** (0.060 g, 83%) was isolated as a white solid: 140-143^{o}C, R_f = 0.42 (EtOAc/Hexane 1 : 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.40 (d, *J* = 9.0 Hz, 1H), 4.07 (dd, *J* = 11.5 Hz, 8.0 Hz, 1H), 3.89 (s, 3H), 3.60 (t, *J* = 11.0 Hz, 1H), 2.75 (sext, *J* = 7.5 Hz, 1H), 2.43 (s, 3H), 2.33-2.27 (m, 1H), 1.29-1.21 (m, 2H), 1.06-1.02 (m, 2H), 0.92 (pent, *J* = 3.5 Hz, 4H), 0.82-0.77 (m, 2H), 0.73 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.6, 22.4, 26.2, 29.1, 29.9, 31.3, 49.7, 52.2, 55.9, 56.3, 68.7, 123.8 (2C), 127.4 (2C), 127.6 (2C), 128.1 (2C), 129.4, 129.8 (2C), 130.1 (2C), 134.9, 143.8, 144.1, 147.3, 149.6, 166.7.

IR (cm^{-1}) 1719; HRMS (ES^{+}): calcd for $C_{31}H_{36}N_2O_6SNa$ $(M+Na)^{+}$ 587.2192, found 587.2206.



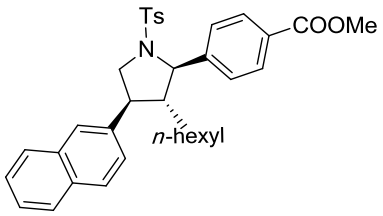
(±)-(2*R*,3*R*,4*S*)-3-(2-Ethylhexyl)-2,4-bis[4-(methoxycarbonyl) phenyl]-1-tosyl pyrrolidine (3.24).

Pyrrolidine **3.24** (0.060 g, 78%) was isolated as colorless oil: R_f = 0.45 (EtOAc–Hexane, 1:5).

^{1}H NMR (500 MHz, CDCl3): δ = 7.96 (dd, *J* = 8.5, 6.5 Hz, 4 H), 7.49 (dd, *J* = 8.5, 6.0 Hz, 2 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 7.0 Hz, 2 H), 4.34 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.13–4.08 (m, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.57 (td, *J* = 11.0, 2.5 Hz, 1 H), 2.76 (qd, *J* = 10.5, 2.0 Hz, 1 H), 2.45–2.36 (m, 1H), 2.40 (s, 3 H), 1.29–1.22 (m, 1 H), 1.20–1.13 (m, 1 H), 0.97–0.86 (m, 2 H), 0.78–0.67 (m, 7 H), 0.67 (t, *J* = 7.0 Hz, 3 H), 0.37 (dt, *J* = 10.0, 3.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.1, 13.94 (13.95), 14.2, 21.5, 22.7 (22.8), 25.31 (25.39), 28.2, 32.3 (32.4), 35.71 (35.79), 36.15 (36.25), 51.5, 52.15 (52.12), 53.65 (53.60), 56.39 (56.30), 70.50 (70.44), 127.29 (127.31) (2 C), 127.53 (127.56) (2 C), 127.75 (127.78) (2 C), 129.31, 129.38, 129.54 (2 C), 129.75 (2 C), 130.04 (2 C), 135.58 (135.63), 143.54, 144.36 (144.44), 146.95 (147.00), 166.69, 166.82; signals for the minor diastereomer arising from the stereocenter in the side chain are given in parentheses.

IR (neat): 1722 cm^{-1}; HRMS (ES^+): calcd for $C_{35}H_{43}NO_6SNa$ $(M + Na)^+$ 628.2709, found 628.2702.

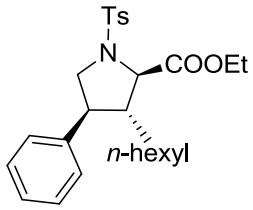


(±)-(2*R*,3*R*,4*S*)-*N*-toluenesulfonyl-3-(1-hexyl)-2-(*p*-methoxycarbonylphenyl)-4-(2-naphthyl)-pyrrolidine (3.25).

Pyrrolidine **3.25** (0.042 g, 86%) was isolated as a colorless oil: R_f = 0.3 (EtOAc/Hexane 1 : 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.81-7.76 (m, 3 H), 7.59 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.49-7.46 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.30 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.16 (dd, *J* = 11.0 Hz, 7.5 Hz, 1H), 3.93 (s, 3H), 3.67 (t, *J* = 11.0 Hz, 1H), 2.91 (sext, *J* = 8.0 Hz, 1H), 2.48-2.40 (m, 1H), 2.44 (s, 3H), 1.34-1.29 (m, 2H), 1.07-1.00 (m, 2H), 0.93-0.90 (m, 4H), 0.89-0.84 (m, 2H), 0.71 (t, *J* = 5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.6, 22.4, 26.1, 29.3, 30.1, 31.3, 50.0, 52.1, 55.7, 56.5, 69.2, 125.2, 125.9, 126.3, 126.7, 127.3 (2C), 127.4 (2C), 127.5, 127.7, 128.6, 129.3, 129.6 (2C), 129.8 (2C), 132.7, 133.4, 135.7, 136.1, 143.5, 147.5, 166.9; IR (cm^{-1}) 1721; HRMS (ES^+): calcd for $C_{35}H_{39}NO_4SNa$ $(M+Na)^+$ 592.2498, found 592.2489.



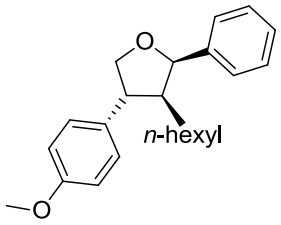
(±)-(2*R*,3*R*,4*S*)-*N*-toluenesulfonyl-3-(1-hexyl)-2-(ethoxycarbonyl)-4-(phenyl)-pyrrolidine (3.33) using Mitsunobu conditions.

To a solution of amino alcohol **3.33** (0.011 g, 0.023 mmol, 1 equiv) in dry THF (1.5 mL) at 0^{o}C was added triphenylphosphine (0.006 g, 0.023 mmol, 1 equiv) and DEAD (4 μL, 0.025 mmol, 1.1 equiv). The solution was stirred at 0^{o}C for 8 h, directly loaded on silica and purified using flash column chromatography eluting with EtOAc/Hexane (1 : 10) to afford pyrrolidine **3.33** (0.009 g, 84%) as a colorless oil: R_f = 0.65 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.34-7.23 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.26-4.21 (m, 2H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.87 (dd, *J* = 10.8 Hz, *J* = 8 Hz, 1H), 3.47 (t, *J* = 10.8 Hz, 1H), 2.73-2.66 (m, 1H), 2.47 (m, 4H), 1.42-1.35 (br, 2H), 1.37 (t, *J* = 7.2, 3H) 1.24-1.01 (m, 8H), 0.84 (t, *J* = 7.2, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 13.0, 20.5, 21.4, 25.5, 28.1, 30.4, 30.6, 49.6, 50.6, 54.3, 60.4, 65.0, 126.3, 126.5 (2C), 126.6 (2C), 127.7 (2C), 128.6 (2C), 134.5, 137.5, 142.6, 171.2.

IR (cm^{-1}) 1741; HRMS (ES^{+}): calcd for $C_{26}H_{35}NO_4SNa$ (M+Na^{+}) 480.2185, found 480.2165.

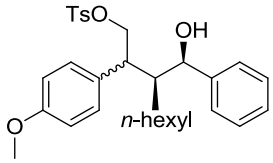


(±)-(2*R*,3*S*,4*R*)-2-phenyl-3-(1-hexyl)-4-(*p*-methoxyphenyl)-tetrahydrofuran (3.36a).

Tetrahydrofuran **3.36a** (0.075 g, 65%) was isolated as a colorless oil: R_f = 0.7 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.30 (d, *J* = 8.0 Hz, 1H), 4.48 (t, *J* = 8.4 Hz, 1H), 3.92 (t, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 3.18 (q, *J* = 8.8 Hz, 1H), 2.48 (quintet, *J* = 7.2 Hz, 1H), 1.19-0.96 (m, 8H), 0.93-0.85 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 27.9, 29.2, 29.4, 31.5, 49.8, 51.5, 55.2, 75.0, 84.1, 114.0 (2C), 126.8 (2C), 127.1, 127.9 (2C), 128.7, 133.2, 140.8 (2C), 158.3; IR (cm^{-1}) 1610, 1514, 1249; HRMS (FAB): calcd for $C_{23}H_{30}O_2$ $(M)^+$ 338.2246, found 338.2254.



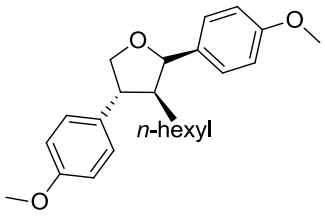
Analytical data for the monotosyldiol 3.37a: R_f = 0.5 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2 H), 7.31-7.23 (m, 4.0 H), 7.20 (t, *J* = 7.2 Hz, 3.0 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.58 (d, *J* =

2.4 Hz, 1.0 H), 4.34 (dd, *J* = 9.6 Hz, *J* = 4.8 Hz, 1.0 H), 4.25 (dd, *J* = 9.6 Hz, *J* = 7.6 Hz, 1.0 H), 3.82 (s, 3.0 H), 3.06 (sextet, *J* = 4.4 Hz, 1.0 H), 2.35 (s, 3.0 H), 1.94-1.89 (m, 1.0 H), 1.64-1.48 (br, 1 H), 1.50-1.39 (m, 2 H), 1.23-1.12 (m, 4 H), 1.09-0.86 (m, 4 H), 0.82 (t, *J* = 7.2 Hz, 3.0 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.6, 25.5, 28.4, 29.4, 31.4, 45.8, 47.1, 55.2, 72.3, 73.12, 114.1 (2C), 125.3 (2C), 126.8, 127.8 (2C), 128.1 (2C), 129.1 (2C), 129.6 (2C), 132.2, 132.7, 143.7, 144.5, 158.5.

IR (neat, cm^{-1}) 3413 (w br), 1512 (s), 1176 (s); HRMS (ES^+) calcd for $C_{30}H_{38}O_5SNa$ ($M+Na^+$), 533.2338, found 533.2341.



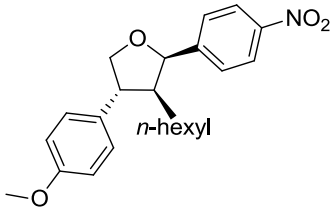
(±)-(2*R*,3*S*,4*R*)-2-(*p*-methoxyphenyl)-3-(1-hexyl)-4-(*p*-methoxyphenyl)-tetrahydrofuran (3.36b).

Tetrahydrofuran **3.36b** (0.048 g, 73%) was isolated as a colorless oil: R_f = 0.7 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 4H, 6.90 (dd, *J* = 8.8 Hz, *J* = 2.4, 4H), 5.25 (d, *J* = 8.0 Hz, 1H), 4.45 (t, *J* = 8.4 Hz, 1H), 3.89 (t, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.16 (q, *J* = 8.8 Hz, 1H), 2.44 (quintet, *J* = 7.6 Hz, 1H), 1.21-0.9 (m, 8H), 0.93-0.86 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 27.9, 29.2, 29.5, 31.5, 49.9, 51.5, 55.24, 55.27, 74.9, 83.8, 113.3 (2C), 114.0 (2C), 128.0 (2C), 128.7 (2C), 132.9, 133.1, 158.3, 158.7.

IR (cm^{-1}) 1612, 1512, 1247; HRMS (ES^+): calcd for $C_{24}H_{33}O_3$ $(M+H)^+$ 369.2430, found 369.2404.

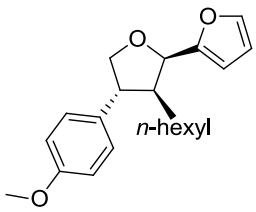


(±)-(2*R*,3*S*,4*R*)-2-(*p*-nitrophenyl)-3-(1-hexyl)-4-(*p*-methoxyphenyl)-tetrahydrofuran (3.36c).

Tetrahydrofuran **3.36c** (0.033 g, 65%) was isolated as a colorless oil: R_f = 0.5 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.35 (d, *J* = 7.6 Hz, 1H), 4.49 (t, *J* = 8.4 Hz, 1H), 3.97 (t, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 3.19 (q, *J* = 8.0 Hz, 1H), 2.53 (quintet, *J* = 7.2 Hz, 1H), 1.21-0.94 (m, 10H), 0.80 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.4, 27.8, 29.1, 29.7, 31.5, 49.8, 51.6, 55.3, 74.9, 83.0, 114.1 (2C), 123.3 (2C), 127.5 (2C), 128.5 (2C), 132.8, 147.1, 148.5, 158.5; IR (cm^{-1}) 1606, 1514, 1346, 1249; HRMS (FAB): calcd for $C_{23}H_{29}O_4$ $(M)^+$ 383.2097, found 338.2095.



(±)-(2*R*,3*S*,4*R*)-2-furyl-3-(1-hexyl)-4-(*p*-methoxyphenyl)-tetrahydrofuran (3.36d). Tetrahydrofuran **3.36d** (0.038 g, 60%) was isolated as a colorless oil: R_f = 0.65 (EtOAc/Hexane 1 : 7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 0.8 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.39-6.33 (m, 1H), 6.29 (d, *J* = 3.2 Hz, 1H), 5.27 (d, *J* = 7.6 Hz, 1H), 4.43 (t, *J* = 8.4 Hz, 1H), 3.88-3.80 (m, 1H), 3.82 (s, 3H), 3.35 (q, *J* = 8.8 Hz, 1H), 2.56-2.44 (m, 1H), 1.25-0.91 (m, 10H), 0.82 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 28.0, 28.4, 29.3, 31.4, 49.7, 51.3, 55.2, 75.2, 77.8, 108.1, 109.9, 114.0 (2C), 128.8 (2C), 132.3, 142.0, 154.5, 158.4.

IR (cm^{-1}) 1610, 1514, 1249; HRMS (FAB): calcd for $C_{21}H_{28}O_3$ $(M)^+$ 328.2038, found 328.2061.

Preparation of tetrahydrofuran 3.36a by Mitsunobu conditions:

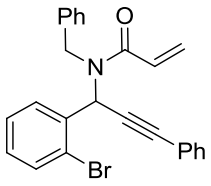
(±)-(2*R*,3*S*,4*R*)-2-phenyl-3-(1-hexyl)-4-(*p*-methoxyphenyl)-tetrahydrofuran (3.36a).

To a solution of diol **3.35a** (0.03 g, 0.084 mmol, 1 equiv) in dry THF (3.0 mL) at 0^{o}C under argon was added triphenylphosphine (0.022 g, 0.084 mmol, 1 equiv) and DEAD (13 μL, 0.084 mmol, 1.0 equiv). The solution was stirred at 0^{o}C for 2.5 h. The reaction mixture was directly loaded on silica and purified using flash column

chromatography eluting with EtOAc/Hexane (1 : 10) to afford an inseparable mixture of diastereomeric furans **3.36a** (0.024 g, 85%) as a colorless oil. The ratio of diastereomers was measured by GC (dr 9 : 1) (See GC in appendix).

General procedure for Cu-catalyzed 3-component coupling reactions to afford 1,6-enynes 4.5, 4.6 and **4.9a-e** and **1,7-enynes 4.9f-j**: **Conditions-A**

Imines (1.0 equiv), benzoyl chloride (1.5 equiv) and alkynes (1.5 equiv) were mixed in acetonitrile (5-10 mL) and stirred for 5 min at rt under argon. The resulting yellow solution and Et*i*Pr$_2$N (1.5 equiv) were added dropwise simultaneously to a solution of CuCl (0.2 equiv) in acetonitrile (2 mL). The reaction mixture was allowed to stir at rt under argon for 2h. Solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over basic alumina eluting with EtOAc/Hexanes mixtures to yield pure enynes **4.5, 4.6** and **4.9a-j**.



***N*-benzyl-*N*-(1-(2-bromophenyl)-3-phenyl) prop-2-yn-1-yl) acrylamide (4.5)**.

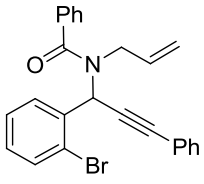
The treatment of imine **4.4** (0.43 g, 1.58 mmol, 1.0 equiv), acryloyl chloride (195 µL, 2.37 mmol, 1.5 equiv) and phenylacetylene (225 µL, 2.37 mmol, 1.5 equiv) with Et*i*Pr$_2$N (410 µL, 2.37 mmol, 1.5 equiv) and CuCl (0.031 g, 0.32 mmol, 0.2 equiv) according to the general procedure described above, followed by flash

chromatography over basic alumina eluting with EtOAc/Hexane (1:4) afforded enyne **4.5** (0.393 g, 58%) as a colorless oil: R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 0.8H), 7.63 (br s, 0.2H), 7.51 (br s, 1H), 6.88-7.43 (m, 12H), 6.50-6.32 (m, 2H), 5.72 (br s, 1H), 4.75-4.44 (m, 2H); In ^{1}H NMR, the signal for the methine proton was not detected due extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**).

^{13}C NMR (125 MHz, $CDCl_3$) δ (48.0), 48.1, (49.9), 50.9, (85.4), 85.6, 86.4, (86.9), (122.3), 124.5, 126.1 (2C), 127.0, 127.3, 127.8, 128.1, 128.2 (2C), (128.40), 128.46, (128.5), 128.6, (129.6), (129.8), 130.0, 131.0, 131.5, 131.7 (2C), 133.3 (2C), (135.8), 137.5, (137.6), 138.0, 166.6, (166.8); Signals for the minor rotamer are given in the parentheses; Significant broadening of some signals in ^{1}H and ^{13}C NMR arises due to hindered rotation about the amide bond. Temperature dependent ^{1}H NMR spectra were recorded (*vide infra*).

IR (cm^{-1}) 1654, 1490, 1425; HRMS (ES^+): calcd for $C_{25}H_{21}BrNO$ $(M+H)^+$ 430.0807, found 430.0812.



***N*-allyl-*N*-(1-(2-bromophenyl)-3-phenyl) prop-2-yn-1-yl) benzamide (4.9a)**.

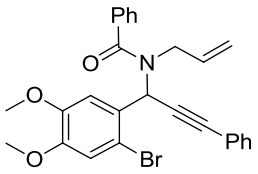
The treatment of imine **4.8a** (0.33 g, 1.48 mmol, 1.0 equiv), benzoyl chloride (260 µL, 2.22 mmol, 1.5 equiv) and phenylacetylene (210 µL, 2.22 mmol, 1.5 equiv) with

$EtNiPr_2$ (385 µL, 2.22 mmol, 1.5 equiv) and CuCl (0.055 g, 0.55 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:4) afforded enyne **4.9a** (0.349 g, 55%) as a light yellow solid: mp 98-101^{o}C; R_f = 0.55 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.79 (br s, 1H), 7.67-7.57 (m, 4H), 7.49-7.33 (m, 7H), 7.25 (t, *J* = 6.8 Hz, 1H), 7.09 (br s, 0.5H), 6.08 (br s, 0.5H), 5.62 (br s, 1H), 4.86 (d, *J* = 10 Hz, 1.5H), 4.77 (br s, 0.5H), 4.01 (br s, 1.5H), 3.66 (br s, 0.5H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 49.5, 50.8, 86.0, 116.5, 122.3, 124.6, 127.3 (2C), 127.5, 128.2 (2C), 128.4, 128.7, 129.8, 130.2, 131.70, 131.76 (2C), 133.4 (2C), 134.1, 135.4, 136.1, 170.7; Significant broadening of some signals in ^{1}H and ^{13}C NMR arises due to hindered rotation about the amide bond. Temperature dependent ^{1}H NMR spectra were recorded (*vide infra*). In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2223, 1643, 1394; HRMS (ES^{+}): calcd for $C_{25}H_{21}BrNO$ $(M+H)^{+}$ 430.0807, found 430.0808.



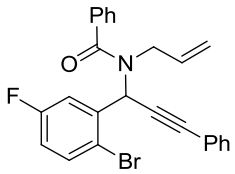
***N*-allyl-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)-3-phenyl) prop-2-yn-1-yl) benzamide (4.9b)**.

The treatment of imine **4.8b** (0.275 g, 0.97 mmol, 1.0 equiv), benzoyl chloride (170 µL, 1.46 mmol, 1.5 equiv) and phenylacetylene (139 µL, 1.46 mmol, 1.5 equiv) with Et*i*Pr$_2$ (255 µL, 1.46 mmol, 1.5 equiv) and CuCl (0.029 g, 0.28 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:3) afforded enyne **4.9b** (0.232 g, 49%) as a light yellow oil: R_f = 0.46 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (br s, 1.75H), 7.55 (t, *J* = 4.0 Hz, 3.25H), 7.49-7.34 (m, 6H), 7.06 (br s, 1H), 6.01 (br s, 1H), 5.69 (br s, 1H), 4.91 (d, *J* = 8.4 Hz, 1.25H), 4.83 (br s, 0.75H), 4.05 (br s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.70 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 42.4, (45.9), 49.3, (50.3), (56.0), 56.1, (56.2), 56.3, 86.4, 114.4, 114.8, 115.8, 116.3, 122.4, 127.2, 128.2 (2C), 128.5 (2C), 128.6, 128.8, 129.8, 131.6 (2C), 134.4, 136.2 (2C), 148.0, 149.7, 171.5; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 1643, 1477, 1236, 1035; HRMS (ES$^+$): calcd for $C_{27}H_{25}BrNO_3$ $(M+H)^+$ 490.1018, found 490.1018.



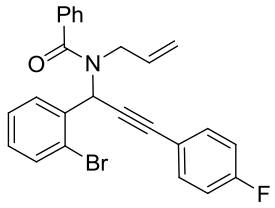
***N*-allyl-*N*-(1-(2-bromo-5-fluorophenyl)-3-phenyl) prop-2-yn-1-yl) benzamide (4.9c)**.

The treatment of imine **4.8c** (0.276 g, 1.14 mmol, 1.0 equiv), benzoyl chloride (200 µL, 1.71 mmol, 1.5 equiv) and phenylacetylene (165 µL, 1.71 mmol, 1.5 equiv) with Et*i*Pr$_2$ (295 µL, 1.71 mmol, 1.5 equiv) and CuCl (0.022 g, 0.22 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:9) afforded enyne **4.9c** (0.264 g, 52%) as a colorless heavy oil: R_f = 0.65 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 9.6 Hz, *J* = 3.2 Hz 1H), 7.60-7.53 (m, 4H), 7.49-7.36 (m, 7H), 6.99 (dt, *J* = 8.4 Hz, *J* = 2.8 Hz 1H), 5.63 (br s, 1H), 4.88 (dd, *J* = 10.0 Hz, *J* = 0.8 Hz 1H), 4.81 (br s, 1H), 4.06-3.97 (m, 1H), 3.79 (br s, 1H); In ^{1}H NMR the signal for methine proton could not be detected likely due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**).

^{13}C NMR (125 MHz, $CDCl_3$) δ (46.2), 49.4, 50.5, (55.9), 85.2, 116.8, 117.2 (d, *J* = 22.3 Hz), 118.5 (d, *J* = 3.2 Hz), 119.0 (d, *J* = 24.5 Hz), (122.0), 125.5, 126.8, (127.3), 128.2 (2C), (128.44), 128.49 (2C), 128.7 (d, *J* = 26.1 Hz), 128.9, 129.9, 130.0, (130.4), 131.8 (2C), (133.8), 134.5 (d, *J* = 7.7 Hz), 135.9 (2C), (137.9), 161.8 (d, *J* = 246.2 Hz), 171.7; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 1647, 1467; HRMS (ES^+): calcd for $C_{25}H_{20}BrFNO$ $(M+H)^+$ 448.0712, found 448.0707.



***N*-allyl-*N*-(1-(2-bromophenyl)-3-(4-fluorophenyl) prop-2-yn-1-yl) benzamide (4.9d)**.

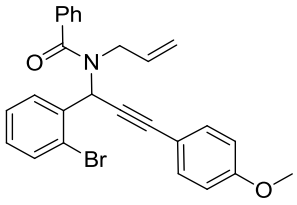
The treatment of imine **4.8a** (0.212 g, 0.95 mmol, 1.0 equiv), benzoyl chloride (165 µL, 1.42 mmol, 1.5 equiv) and *p*-fluorophenylacetylene (0.171 g, 1.42 mmol, 1.5 equiv) with Et*i*Pr_2 (210 µL, 1.42 mmol, 1.5 equiv) and CuCl (0.019 g, 0.19 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:9) afforded enyne **4.9d** (0.225 g, 53%) as a light white solid: mp 89- 93^oC; R_f = 0.72 (EtOAc/Hexane 3:7).

^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.61 (br s, 2H), 7.58-7.50 (m, 3H), 7.49-7.36 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.09 (br s, 1H), 5.62 (br s, 1H), 4.86 (dd, *J* = 10.0 Hz, *J* = 1.2 Hz 1H), 4.77 (br s, 1H),

4.01 (d, *J* = 14.0 Hz, 1H), 3.70 (br s, 1H); In ^1H NMR, the signal for methine proton appeared to integrate for only 0.1H due to extensive broadening (see the temperature dependent ^1H NMR spectra for **4.9a**). However the signal was recorded as 1H (6.09 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 46.3, (49.0), 50.4, (56.1), 85.7, 115.7 (d, *J* = 21.8 Hz, 2C), 116.5, 118.4, 124.6, 127.2, 127.3 (2C), 128.2 (2C), 129.8, 130.2 (d, *J* = 43.8 Hz), 131.6, 133.4, 133.7 (d, *J* = 8.3 Hz, 2C), 133.9, 135.3, 136.1, 162.7 (d, *J* = 248.6 Hz), 171.7; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2227, 1643, 1506; HRMS (ES^+): calcd for $C_{25}H_{20}BrFNO$ $(M+H)^+$ 448.0712, found, 448.0707.



***N*-allyl-N-(1-(2-bromophenyl)-3-(4-methoxyphenyl) prop-2-yn-1-yl) benzamide (4.9e)**.

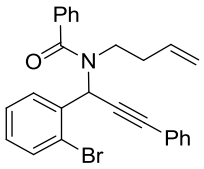
The treatment of imine **4.8a** (0.15 g, 0.673 mmol, 1.0 equiv), benzoyl chloride (120 µL, 1.01 mmol, 1.5 equiv) and *p*-methoxyphenylacetylene (122 µL, 1.01 mmol, 1.5 equiv) with Et*i*Pr_2 (0.13 g, 174 µL, 1.01 mmol, 1.5 equiv) and CuCl (0.013 g, 0.135 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:4) afforded enyne **4.9e** (0.19 g, 61%) as a colorless heavy oil: R_f = 0.55 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 1H), 7.82 (br s, 1H), 7.59 (br s, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.47-7.35 (m, 4H), 7.24 (t, *J* = 6.8 Hz, 1H), 7.08 (br s, 0.5H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.05 (br s, 0.5H), 5.61 (br s, 1H), 4.84 (d, *J* = 10.4

Hz, 1H), 4.7 (br s, 1H), 3.98 (br s, 1.5H), 3.86 (s, 3H), 3.68 (br s, 0.5H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (7.08 and 6.05 ppm) that integrate for only 0.5H when combined due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**). However the signals were presented herein as 0.5H (7.08 ppm) and 0.5H (6.05 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 44.0, (47.2), 48.6, 53.4, (54.4), 82.6, 112.1, 114.5, 122.6, 125.3 (2C), 125.5, 126.2 (2C), 126.4, 127.9, 128.2, 129.8 (2C), 131.2 (2C), 131.4, 132.1, 133.7, 134.3, 158.0, 169.7; Significant broadening of some signals in ^{1}H and ^{13}C NMR arises due to hindered rotation about the amide bond. Temperature dependent ^{1}H NMR spectra were recorded (*vide infra*). In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2210, 1643, 1396, 1027; HRMS (ES^{+}): calcd for $C_{26}H_{23}BrNO_2$ $(M+H)^{+}$ 460.0912, found 460.0911.



***N*-(1-(2-bromophenyl)-3-phenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9f)**.

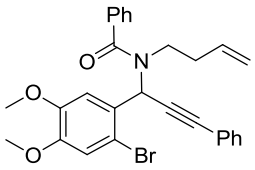
The treatment of imine **4.8d** (0.325 g, 1.36 mmol, 1.0 equiv), benzoyl chloride (235 µL, 2.04 mmol, 1.5 equiv) and phenylacetylene (195 µL, 2.04 mmol, 1.5 equiv) with Et*i*Pr$_2$N (350 µL, 2.04 mmol, 1.5 equiv) and CuCl (0.027 g, 0.27 mmol, 0.2 equiv)

according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:4) afforded enyne **4.9f** (0.332 g, 55%) as a white solid: mp 75-80^{o}C; R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.79 (br s, 1H), 7.69-7.53 (m, 4H), 7.50-7.36 (m, 7H), 7.31-7.23 (m, 1H), 7.06 (br s, 0.5H), 6.05 (br s, 0.5H), 5.80-5.36 (m, 1H), 4.89 (br s, 2H), 3.58-2.86 (m, 2H), 2.46 (br s, 1H), 1.81 (br s, 1H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (7.06 and 6.05 ppm) that integrate for only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H (7.06 ppm) and 0.5H (6.05 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.5, (33.9), 43.3, (46.0), (50.4), 56.2, 86.2, 116.3, (116.7), 122.2, 124.4, 127.1, 127.5 (2C), 127.6, 128.2, 128.41, 128.49, 128.7, (128.8), 129.8, 130.3, 131.3 (2C), 131.7 (2C), 133.5 (2C), (135.5), 136.4, 171.6; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2223, 1641, 1402; HRMS (ES^{+}): calcd for $C_{26}H_{22}BrNONa$ $(M+Na)^{+}$ 466.0782, found 466.0778.



***N*-(1-(2-bromo-4,5-dimethoxyphenyl)-3-phenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9g)**.

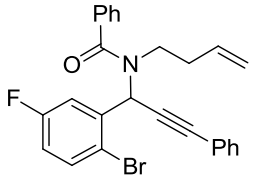
The treatment of imine **4.8e** (0.329 g, 1.11 mmol, 1.0 equiv), benzoyl chloride (190 µL, 1.66 mmol, 1.5 equiv) and phenylacetylene (160 µL, 1.66 mmol, 1.5 equiv) with Et*i*Pr$_2$ (285 µL, 1.66 mmol, 1.5 equiv) and CuCl (0.022 g, 0.22 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:4) afforded enyne **4.9g** (0.248 g, 45%) as a colorless oil: R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.71 (m, 1H), 7.68-7.50 (m, 4H), 7.49-7.33 (m, 6H), 7.08 (br s, 1H), 7.05 (br s, 0.5H) 6.35-5.91 (m, 0.5H), 5.87-5.35 (m, 1H), 5.21-5.10 (m, 0.2H), 4.92 (br s, 1.8H), 3.95(s, 3H), 3.92 (s, 3H), 3.60-2.86 (m, 2H), 2.67-2.25 (m, 1H), 1.88 (br s, 1H); In ^{1}H NMR the signal for the methine proton appeared as a broad singlet and a multiplet (7.05 and 6.35-5.91 ppm) that integrate for only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H (7.05 ppm) and 0.5H (6.35-5.91 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.6, (33.9), 43.1, (46.0), (50.1), 55.9, 56.21, 56.29, 86.6, 114.0, 114.6, (115.2), 115.9, (116.3), 117.4, (122.1), 126.8, (127.5), 128.2 (2C), 128.54 (2C), 128.58, (128.9), 129.8, 131.3, 131.6 (2C), 131.7, (134.7), 135.3, (135.6),

136.4 (2C), 148.1, 149.7, (167.4), 171.5; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2225, 1487, 1280, 1031; HRMS (ES^+): calcd for $C_{28}H_{26}BrNO_3Na$ $(M+Na)^+$ 526.0994, found 526.0985.



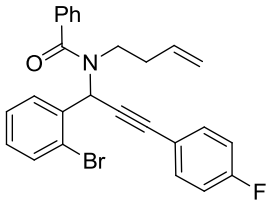
***N*-(1-(2-bromo-5-fluorophenyl)-3-phenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9h)**.

The treatment of imine **4.8f** (0.32 g, 1.25 mmol, 1.0 equiv), benzoyl chloride (215 µL, 1.87 mmol, 1.5 equiv) and phenylacetylene (180 µL, 1.87 mmol, 1.5 equiv) with Et*i*Pr_2 (240 µL, 1.87 mmol, 1.5 equiv) and CuCl (0.025 g, 0.25 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:9) afforded enyne **4.9h** (0.299 g, 52%) as a colorless oil: R_f = 0.6 (EtOAc/Hexane 3:7).

^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.2 Hz, *J* = 1.2 Hz, 0.25H), 7.77 (d, *J* = 7.6 Hz, 1.25H), 7.71 (t, *J* = 7.2 Hz, 0.5H), 7.64-7.52 (m, 4H), 7.50-7.34 (m, 7H), 7.01 (td, *J* = 8.0 Hz, *J* = 2.8 Hz, 1H), 6.20-5.35 (m, 1H), 5.25-4.72 (m, 2H), 3.75-2.90 (m, 2H), 2.49 (br s, 1H), 2.16-2.05 (m, 0.15H), 1.92 (br s, 0.85H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (32.6), 33.8, 43.2, (46.3), (50.3), 56.0, 85.4, [115.4, (d, *J* = 24.7 Hz)], [116.5, (d, *J* = 3.2 Hz)], 117.3, (117.4), 118.3 (d, *J* = 3.3 Hz), 118.6 (d, *J* = 24.3 Hz), 126.8, (127.4), 128.3 (2C), 128.4 (d, *J* = 9.6 Hz), 128.5 (d, *J* = 8.0 Hz), 128.8, (129.0), 129.87 (2C), (129.89), (129.9), 130.3, 131.4, 131.8 (2C), 133.9, 134.8 (d, *J* = 7.7 Hz), [135.0, (d, *J* = 7.8 Hz)], (135.5), 136.2 (2C), (138.0), (164.1), 161.8 (d, *J* = 246.6 Hz), [161.9, (d, *J* = 246.8 Hz)], 171.7, (172.8); Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 1643, 1467; HRMS (ES^+): calcd for $C_{26}H_{22}BrFNO$ $(M+H)^+$ 462.0869, found 462.0877.



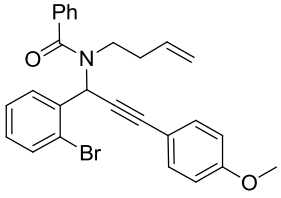
***N*-(1-(2-bromophenyl)-3-(4-fluorophenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9i)**.

The treatment of imine **4.8d** (0.193 g, 0.811 mmol, 1.0 equiv), benzoyl chloride (140 µL, 1.21 mmol, 1.5 equiv) and *p*-fluorophenylacetylene (0.145 g, 1.21 mmol, 1.5 equiv) with Et*i*Pr_2 (210 µL, 1.21 mmol, 1.5 equiv) and CuCl (0.016 g, 0.16 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:9) afforded enyne **4.9i** (0.22 g, 58%) as a colorless oil: R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.86-7.59 (m, 2H), 7.54 (dd, *J* = 5.2 Hz, *J* = 3.2 Hz, 2H), 7.49-7.39 (m, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 2H), 7.03 (br s, 0.5H), 6.03 (br s, 0.5H), 5.83-5.27 (m, 1H), 4.89 (br s, 2H), 3.94-2.86 (m, 2H), 2.40 (br s, 1H), 1.81 (br s, 1H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (7.03 and 6.03 ppm) that integrate for only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H (7.03 ppm) and 0.5H (6.03 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.5, (33.8), 43.3, (46.0), 50.1, (56.1), 85.9, 115.8 (d, *J* = 21.6 Hz, 2C), 116.6, (118.3), 124.4, 125.5, (127.2), 127.5, 128.2, 128.4, 128.6, [128.7 (d, *J* = 5.2 Hz)], 129.8 (d, *J* = 5.2 Hz), 130.5, 131.2 (2C), 133.6 (2C), 133.7 (d, *J* = 8.3 Hz, 2C), (135.4), 136.3, 138.9, 162.8 (d, *J* = 248.6 Hz), (171.0), 172.6; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2225, 1643, 1400; HRMS (ES^{+}): calcd for $C_{26}H_{21}BrFNONa$ $(M+Na)^{+}$ 484.0688, found 484.0685.



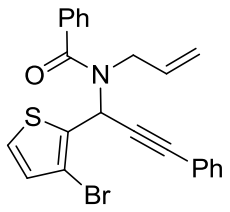
***N*-(1-(2-bromophenyl)-3-(4-methoxyphenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9j)**.

The treatment of imine **4.8d** (0.19 g, 0.798 mmol, 1.0 equiv), benzoyl chloride (140 µL, 1.19 mmol, 1.5 equiv) and *p*-methoxyphenylacetylene (155 µL, 1.19 mmol, 1.5 equiv) with Et*i*Pr$_2$ (205 µL, 1.19 mmol, 1.5 equiv) and CuCl (0.016 g, 0.16 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/hexane (1:4) afforded enyne **4.9j** (0.2 g, 53%) as a colorless oil: R_f = 0.6 (EtOAc/hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.80 (br s, 1H), 7.60 (br s, 2H), 7.50 (d, *J* = 10.4 Hz, 2H), 7.47-7.38 (m, 4H), 7.30-7.22 (m, 1H), 7.04 (br s, 0.5H), 6.92 (d, *J* = 7.2 Hz, 2H), 6.03 (br s, 0.5H), 5.80-5.13 (m, 1H), 4.90 (br s, 2H), 3.86 (s, 3H), 3.56-2.82 (m, 2H), 2.47 (br s, 1H), 1.79 (br s, 1H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (7.04 and 6.03 ppm) that integrate for only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H (7.04 ppm) and 0.5H (6.03 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.4, (33.9), 43.3, (46.0), (50.4), 55.3, 56.3, 84.7, 114.3, 116.2, (116.8), 124.4, 126.9, 127.5 (2C), 128.2, 128.6, 129.8, 130.2, 131.4 (2C), 133.2 (2C), 133.4, 133.5 (2C), 135.6, 136.5, 160.0, 171.6; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2221, 1643, 1510, 1027; HRMS (ES^+): calcd for $C_{27}H_{25}BrNO_2$ $(M+H)^+$ 474.1069, found 474.1072.



***N*-allyl-*N*-(1-(3-bromothiophen-2-yl)-3-phenyl) prop-2-yn-1-yl) benzamide (4.9k)**.

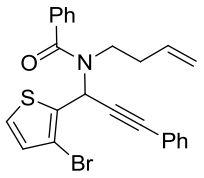
The treatment of imine **4.8g** (0.41 g, 1.78 mmol, 1.0 equiv), benzoyl chloride (310 µL, 2.67 mmol, 1.5 equiv) and phenylacetylene (255 µL, 2.67 mmol, 1.5 equiv) with Et*i*Pr$_2$ (460 µL, 2.67 mmol, 1.5 equiv) and CuCl (0.036 g, 0.36 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/hexane (1:9) afforded enyne **4.9k** (0.48 g, 62%) as a colorless oil: R_f = 0.6 (EtOAc/hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br, s, 1.75H), 7.58-7.53 (m, 2.25H), 7.50-7.35 (m, 6H), 7.29 (d, *J* = 5.6 Hz, 1H), 7.17 (br s, 0.5H), 6.99 (br s, 1H), 6.18 (br s, 0.5H), 5.73 (br s, 1H), 4.93 (d, *J* = 10.0 Hz, 2H), 4.29-3.78 (m, 2H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (7.17 and 6.18 ppm) that integrate for only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**). However the signals were presented herein as 0.5H (7.17 ppm) and 0.5H (6.15 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 45.2, (46.0), 49.2, (50.9), 85.5, 110.9, 116.4, 121.9, 126.0, 127.3, 128.3 (2C), 128.4 (2C), 129.2, 130.0, 131.0 (2C), 131.8 (2C), 132.0,

133.8, 135.8, 171.4; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2223, 1643, 1394; HRMS (ES^+): calcd for $C_{23}H_{18}BrNOSNa$ $(M+Na)^+$ 458.0190, found 458.0199.



***N*-(1-(3-bromothiophen-2-yl)-3-phenylprop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9l)**.

The treatment of Imine **4.8h** (0.32 g, 1.32 mmol, 1.0 equiv), benzoyl chloride (230 µL, 1.98 mmol, 1.5 equiv) and phenylacetylene (189 µL, 1.98 mmol, 1.5 equiv) with Et*i*Pr_2 (342 µL, 1.98 mmol, 1.5 equiv) and CuCl (0.026 g, 0.26 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over basic alumina eluting with EtOAc/Hexane (1:9) afforded enyne **4.9l** (0.355 g, 60%) as a yellow oil: R_f = 0.65 (EtOAc/Hexane 1:7);

^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.82 (br, 1.5H), 7.60-7.54 (m, 2.5H), 7.52-7.35 (m, 6H), 7.32 (d, *J* = 5.2 Hz, 1H), 7.19 (br, s, 0.5H), 7.09-6.94 (br, 1H), 6.11 (br, s, 0.5H), 5.93-5.36 (br, 1H), 5.11-4.75 (br, 2H), 3.80-3.14 (br, 2H), 2.30-2.67 (br, 1H), 2.20-1.96 (m, 1H); In ^1H NMR the signal for the methine proton appeared as two broad singlets (7.19 and 6.11 ppm) that integrate for only 0.75H when combined, due

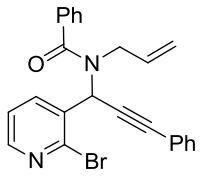
to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H.

^{13}C NMR (125 MHz, $CDCl_3$) δ 32.7, (34.0), 43.3, (45.0), 46.0, (51.0), 85.8, 110.8, 116.5, 121.8, 125.5, 126.1, 127.3, 128.42 (2C), 128.49 (2C), 129.0, 129.9, 131.1 (2C), 131.8 (2C), 135.5, 136.1, 171.4; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 2226, 1647, 1436; HRMS (ES^{+}): calcd for $C_{24}H_{20}BrNOSNa$ $(M+Na)^{+}$ 472.0347 found 472.0340.

General procedure for Cu-catalyzed 3-component-coupling reactions to afford enynes 4.8m-o and 4.9p-r: Condition B

Imine (1.0 equiv), benzoyl chloride (1.2 equiv) and phenylacetylene (1.2 equiv) were mixed in acetonitrile (5 mL) and stirred at rt under argon for 5 min to afford a yellow solution. To this solution neat Et*i*Pr$_2$ (1.2 equiv) and the solution of CuCl (0.2 equiv) in acetonitrile (1 mL) were added simultaneously dropwise. The reaction mixture was allowed to stir at rt under argon for 1 h. Solvents were removed under reduced pressure and the resulting crude product was separated by flash chromatography over silica eluting with EtOAc/Hexanes mixtures to yield pure enynes **4.8m-o** and **4.9p-r**.



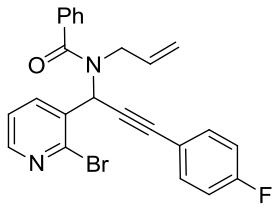
***N*-allyl-*N*-(1-(2-bromopyridin-3-yl)-3-phenylprop-2-yn-1-yl) benzamide (4.9m)**.

The treatment of imine **4.8i** (0.12 g, 0.53 mmol, 1.0 equiv), benzoyl chloride (0.091 g, 75 µL, 0.64 mmol, 1.2 equiv) and phenylacetylene (0.065 g, 61 µL, 0.64 mmol, 1.2 equiv) with Et*i*Pr$_2$ (0.082 g, 110 µL, 0.64 mmol, 1.2 equiv) and CuCl (0.011 g, 0.11 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded enyne **4.9m** (0.135 g, 59%) as a colorless oil: R_f = 0.4 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.6 Hz, *J* = 1.6 Hz, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.65 (br s, 1.5H), 7.56 (dd, *J* = 7.6 Hz, *J* = 2.4 Hz, 2.5H), 7.50-7.39 (m, 5.75H), 7.37 (dd, *J* = 7.6 Hz, *J* = 4.4 Hz, 1.25H), 5.69 (br s, 1H), 4.87 (d, *J* = 10.4 Hz, 1H), 4.76 (dd, *J* = 17.2 Hz, *J* = 1.2 Hz, 1H), 4.29-3.56 (m, 2H); In ^{1}H NMR the signal for the methine proton was not detected due extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**).

^{13}C NMR (125 MHz, $CDCl_3$) δ 50.1, 55.8, 84.7, 99.9, 116.8, 121.9, 122.5 (2C), 127.3, 128.3 (2C), 128.5 (2C), 129.0, 130.1, 131.8(2C), 133.4, 133.9, 135.7, 139.9, 144.0, 149.8, 171.8; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 2223, 1643, 1400; HRMS (ES$^+$): calcd for $C_{24}H_{19}BrN_2ONa$ $(M+Na)^+$ 453.0578, found 453.0571.



***N*-allyl-*N*-(1-(2-bromopyridin-3-yl)-3-(4-fluorophenyl)prop-2-yn-1-yl) benzamide (4.9n)**.

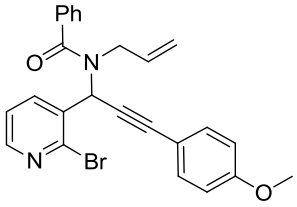
The treatment of imine **4.8i** (0.12 g, 0.53 mmol, 1.0 equiv), benzoyl chloride (0.091 g, 75 µL, 0.64 mmol, 1.2 equiv) and *p*-fluorophenylacetylene (0.076 g, 73 µL, 0.64 mmol, 1.2 equiv) with Et*i*Pr$_2$ (0.082 g, 110 µL, 0.64 mmol, 1.2 equiv) and CuCl (0.011 g, 0.11 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded enyne **4.9n** (0.142 g, 60%) as a colorless oil: R_f = 0.4 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 8.27 (d, *J* = 6.0 Hz, 1H), 7.83 (br s, 0.75H), 7.77-7.31 (m, 7.25H), 7.09 (t, *J* = 7.6 Hz, 2H), 6.91 (br s, 0.5H), 6.40 (br s, 0.5H), 5.98 (br, 0.30H), 5.68 (br s, 0.70H), 5.25 (dd, *J* = 34.8 Hz, *J* = 16.8 Hz, 0.5H), 4.82 (dd, *J* = 42.8 Hz, *J* = 9.6 Hz, 1.5H), 4.42-4.72 (m, 2H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (6.91 and 6.40 ppm) that integrate for only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**). However the signals were presented herein as 0.5H (6.91 ppm) and 0.5H (6.40 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 33.1, 84.4, 99.9, 115.8 (d, *J* = 22.0 Hz), 116.7, (116.9), (118.0), 122.6 (2C), (123.4), 126.9 (2C), 127.3, 128.5 (d, *J* = 27.3 Hz, 2C), 130.2, 131.5, (133.3), 133.8 (d, *J* = 9.3 Hz, 2C), 133.9, (134.2), 135.6, (138.0), 139.8,

144.0, 149.8, (154.5), 162.9 (d, J = 249.4 Hz), 171.9; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 2223, 1643, 1400; HRMS (ES^+): calcd for $C_{24}H_{18}BrFN_2ONa$ $(M+Na)^+$ 471.0484, found 471.0487.



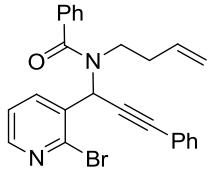
***N*-allyl-*N*-(1-(2-bromopyridin-3-yl)-3-(4-methoxyphenyl)prop-2-yn-1-yl) benzamide (4.9o)**.

The treatment of imine **4.8i** (0.14 g, 0.63 mmol, 1.0 equiv), benzoyl chloride (103µL, 0.76 mmol, 1.2 equiv) and *p*-methoxyphenylacetylene (99 µL, 0.76 mmol, 1.2 equiv) with Et*i*Pr_2 (1320 µL, 0.76 mmol, 1.2 equiv) and CuCl (0.013 g, 0.12 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:2) afforded enyne **4.9o** (0.180 g, 62%) as a colorless oil: R_f = 0.35 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 4.4 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H), 7.53-7.40 (m, 5H), 7.34 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 5.69 (br, 1H), 4.85 (d, J = 10.0 Hz, 1H), 4.74 (dd, J = 17.2 Hz, J = 1.2 Hz, 1H), 3.96 (br s, 1.5H), 1.5H), 3.88 (br, 0.5H), 3.86 (s, 3H); In ^{1}H NMR the signal for the methine proton was not observed due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9a**).

^{13}C NMR (125 MHz, $CDCl_3$) δ 50.0, 55.4, 83.3, 113.8, 114.1 (2C), 116.8, 122.5 (2C), 127.3, 128.3 (2C), 130.1, 133.2 (2C), 133.5, 134.0, 135.8, 139.9, 144.0, 149.7, 160.1, 171.8.

IR (cm^{-1}) 2213, 1643, 1249; HRMS (ES^+): calcd for $C_{25}H_{21}BrN_2O_2Na$ $(M+Na)^+$ 483.0684, found 483.0692.



***N*-(1-(2-bromopyridin-3-yl)-3-phenylprop-2-yn-1-yl)-*N*-(but-3-en-1-yl) enzamide (4.9p)**.

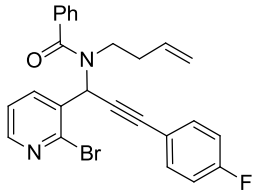
The treatment of imine **4.8j** (0.12 g, 0.5 mmol, 1.0 equiv), benzoyl chloride (0.084 g, 70 µL, 0.6 mmol, 1.2 equiv) and phenylacetylene (0.061 g, 57 µL, 0.6 mmol, 1.2 equiv) with Et*i*Pr$_2$ (0.078 g, 104 µL, 0.6 mmol, 1.2 equiv) and CuCl (0.010 g, 0.1 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded enyne **4.9p** (0.137 g, 62%) as a colorless oil: R_f = 0.4 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.4 Hz, *J* = 1.2 Hz, 1H), 8.32 (d, *J* = 5.4 Hz, 1H), 7.67 (br s, 2H), 7.56 (dd, *J* = 7.6 Hz, *J* = 2.4 Hz, 2H), 7.52-7.36 (m, 7H), 6.83 (br s, 0.5H), 6.05 (br s, 0.5H), 5.60 (br s, 1H), 4.97-4.81 (m, 2H), 3.55-3.43 (m, 1H), 3.25 (br s, 1H), 2.47 (br s, 1H), 1.95 (br s, 1H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (6.83 and 6.05 ppm) that integrate for

only 0.5H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H (6.83 ppm) and 0.5H (6.05 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 33.0, (33.6), 43.5, (47.0), 50.0, (55.4), 84.8, 117.0, 121.8, 122.7 (2C), 127.2, 128.3 (2C), 128.5 (2C), 128.8, 129.1, 129.8, 130.0, 131.7 (2C), 136.0, 139.5, 143.8, 149.8, 171.8; Signals for the minor rotamer are given in parentheses; In ^{13}C NMR spectra only one signal for the two sp carbons was observed.

IR (cm^{-1}) 1637, 1490, 1446; HRMS (ES^{+}): calcd for $C_{25}H_{21}BrN_2ONa$ $(M+Na)^{+}$ 467.0735, found 467.0741.



***N*-(1-(2-bromopyridin-3-yl)-3-(4-fluorophenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9q)**.

The treatment of imine **4.8j** (0.15 g, 0.627 mmol, 1.0 equiv), benzoyl chloride (0.128 g, 106 µL, 0.752 mmol, 1.2 equiv) and *p*-fluorophenylacetylene (0.092 g, 87 µL, 0.752 mmol, 1.2 equiv) with Et*i*Pr$_2$ (0.072 g, 97 µL, 0.752 mmol, 1.2 equiv) and CuCl (0.013 g, 0.13 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane

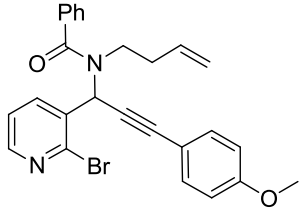
(1:3) afforded enyne **4.9q** (0.175 g, 61%) as a colorless oil: R_f = 0.4 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.8 Hz, *J* = 2.0 Hz, 1H), 8.30 (br s, 1H), 7.78-7.58 (m, 2H), 7.57-7.51 (m, 2H), 7.49-7.37 (m, 4H), 7.10 (t, *J* = 8.4 Hz, 2H), 5.95-5.38 (m, 1H), 4.90 (dd, *J* = 22.8 Hz, *J* = 10.4 Hz, 2H), 3.60-3.40 (m, 1.25H), 3.23 (br s, 0.75H), 2.55-2.34 (m, 1H), 1.95 (br s, 1H); In ^{1}H NMR the signal for the methine proton was not observed.

^{13}C NMR (125 MHz, $CDCl_3$) δ 84.6, 115.9 (d, *J*

= 22 Hz, 2C), (117.0), 117.5, (122.6), 122.7 (2C), 126.7, 127.2, 128.4 (2C), 128.5, 130.0, 131.4, 133.7 (d, *J* = 8.5 Hz, 2C), (135.3), 135.9, 139.4, 143.8, 149.9, 163.0 (d, *J* = 249 Hz), 171.8; In ^{13}C NMR spectra only one signal for the two methylene carbons and only one signal for the two sp carbons was observed. No signal was observed for methine due to significant broadening. Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 2230, 1643, 1506, 1400; HRMS (ES^+): calcd for $C_{25}H_{20}BrFN_2ONa$ $(M+Na)^+$ 485.0641, found 485.0640.



***N*-(1-(2-bromopyridin-3-yl)-3-(4-methoxyphenyl) prop-2-yn-1-yl)-*N*-(but-3-en-1-yl) benzamide (4.9r)**.

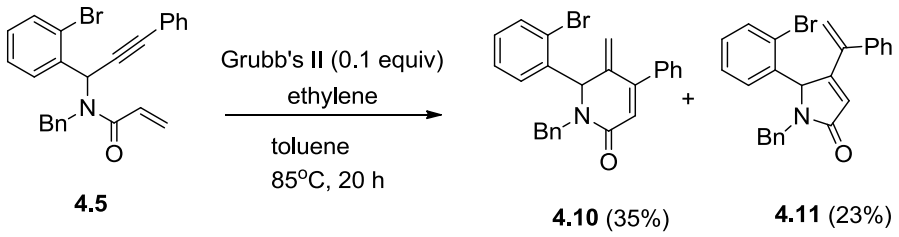
The treatment of imine **4.8j** (0.166 g, 0.694 mmol, 1.0 equiv), benzoyl chloride (0.115 g, 95 µL, 0.832 mmol, 1.2 equiv) and *p*-methoxyphenylacetylene (0.110 g, 108 µL, 0.832 mmol, 1.2 equiv) with Et*i*Pr$_2$ (0.107 g, 144 µL, 0.832 mmol, 1.2 equiv) and CuCl (0.014 g, 0.14 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded enyne **4.9r** (0.207 g, 63%) as a colorless oil: R_f = 0.3 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.4 Hz, *J* = 1.2 Hz, 1H), 8.36-8.26 (m, 1.4H), 7.67 (br, 1.6H), 7.53-7.36 (m, 6H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.91 (br s, 0.5H), 6.80 (d, *J* = 9.2 Hz, 1H), 6.01 (br s, 0.5H), 5.76-5.44 (m, 1H), 5.04-4.76 (m, 2H), 3.86 (s, 2H), 3.82 (s, 1H), 3.57-2.87 (m, 2H), 2.45 (br s, 0.75H), 2.17-1.82 (m, 1.25H); In ^{1}H NMR the signal for the methine proton appeared as two broad singlets (6.91 and 6.01 ppm) that integrate for only 0.7H when combined, due to extensive broadening (see the temperature dependent ^{1}H NMR spectra for **4.9f**). However the signals were presented herein as 0.5H (6.91 ppm) and 0.5H (6.01 ppm).

^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 49.1, 55.33, (55.39), 56.5, (83.4), 83.8, 88.7, 113.8, (113.9), 114.1, (114.6), 115.7, 122.6, 122.7 (2C), (127.3), 128.3 (2C), (130.0), (133.1), 133.2 (2C), 135.9, 136.0, 136.3, 139.6 (2C), (140.6), 143.8, 144.2, 149.1, (149.8), 159.7, 171.8.

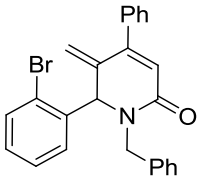
IR (cm^{-1}) 2221, 1641, 1510, 1029; HRMS (ES^+): calcd for $C_{26}H_{24}BrN_2O_2Na$ $(M+H)^+$ 475.1021, found 475.1017.

1-Benzyl-6-(2-bromophenyl)-5-methylene-4-phenyl-5,6-dihydropyridin-2-one (4.10) and **1-Benzyl-5-(2-bromophenyl)-4-(1-phenylvinyl)-pyrrol-2-one (4.11)**.



4.5 **4.10** (35%) **4.11** (23%)

The solution of enyne **4.5** (0.13 g, 0.30 mmol, 1.0 equiv) in toluene (20 mL) was degassed with ethylene for 5 min, Grubb's II catalyst (0.025 g, 0.03 mmol, 0.1 equiv) was added and the reaction mixture was stirred at 85°C under ethylene atmosphere for 20 h. The mixture was cooled to rt, directly loaded on a silica column and purified by flash chromatography, eluting with EtOAc/Hexane (1:9) to afford pure diene **4.10** (0.045 g, 35%) as a colorless heavy oil and continuous elution with EtOAc/Hexane (1:4) afforded pure diene **4.11** (0.03 g, 23%) as a colorless heavy oil.

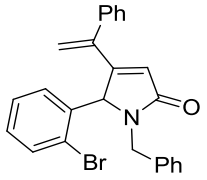


Analytical data for 4.10: R_f = 0.52 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.38-7.31 (m, 8H), 7.25-7.17 (m, 4H), 6.21 (s, 1H), 5.83 (s, 1H), 5.75 (s, 1H), 5.45 (d, *J* = 14.8 Hz, 1H), 5.16 (s, 1H), 3.57 (d, *J* = 14.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 46.1, 61.0, 119.1, 119.6, 121.3, 126.1, 126.2, 126.9, 127.15 (2C), 127.16 (2C), 127.18 (2C), 127.2 (2C), 127.8, 128.3, 132.2, 135.3, 135.5, 137.5, 138.9, 147.0, 162.8.

IR (cm^{-1}) 1689, 1494, 1265; HRMS (ES^+): calcd for $C_{25}H_{21}BrNO$ $(M+H)^+$ 430.0807, found 430.0808.



Analytical data for 4.11: R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.37-7.31 (m, 5H), 7.25-7.16 (m, 7H), 7.07 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 6.13 (s, 1H), 5.90 (s, 1H), 5.38 (s, 1H), 5.26 (s, 1H), 5.01 (d, *J* = 15.2 Hz, 1H), 3.71 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 44.0, 64.2, 120.1, 125.1, 127.3, 127.5, 128.00, 128.03 (2C), 128.2, 128.3 (2C), 128.4 (2C), 128.5 (2C), 130.2, 130.4, 133.2, 135.2, 137.2, 139.4, 141.6, 158.9, 170.8.

IR (cm^{-1}) 1650, 1494, 1261; HRMS (ES^+): calcd for $C_{25}H_{21}BrNO$ $(M+H)^+$ 430.0807, found 430.0803.

General procedure for the preparation of dihydropyrroles 4.12a-h:

The solution of 1,6-enynes **4.9a-e, 4.9k or** or **4.9m-n** (1.0 equiv) in toluene (5-15 mL) was degassed with ethylene for 5 min, Grubb's I catalyst (0.1 equiv) was added

and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 2h. The mixture was cooled to rt, directly loaded on a silica column and purified by flash chromatography eluting with EtOAc/Hexane mixtures to afford pure dihydropyrroles **4.12a-h**.

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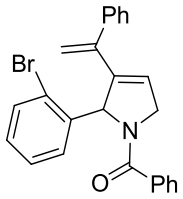


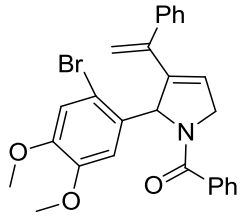
***N*-benzoyl-(2-(2-bromophenyl)-3-(1-phenylvinyl)-2,5-dihydro)-pyrrole (4.12a)**.

The treatment of enyne **4.9a** (0.07 g, 0.16 mmol, 1.0 equiv) with Grubb's I catalyst (0.013 g, 0.016 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded dihydropyrrole **4.12a** (0.065 g, 93%) as colorless oil: R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 6.4 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 3H), 7.35-7.31 (m, 4.3H), 7.24-7.19 (m, 2.7H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.04-6.96 (m, 1H), 6.64 (s, 0.7H), 6.11 (s, 0.3H), 5.92 (s, 0.3H), 5.75 (s, 0.7H), 5.38 (s, 0.7H), 5.28 (s, 0.3H), 5.16 (s, 0.7H), 5.09 (s, 0.3H), 4.84-4.66 (m, 1.3H), 4.27 (d, *J* = 16.0 Hz, 0.7H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (54.3), 56.9, (60.4), 67.6, (116.9), 117.6, 125.0, 125.9, 127.2 (2C), 127.6, 127.7, 128.0, 128.1 (2C), 128.25 (2C), 128.28 (2C), 128.5, 129.1, (129.2), 130.1, 133.5, 136.1, (136.8), 139.5, (140.5), 140.7, 142.1, (142.2), 169.5, (171.1); Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1492, 1469; HRMS (ES^+): calcd for $C_{25}H_{21}BrNO$ $(M+H)^+$ 430.0807, found 430.0801.



***N*-benzoyl-(2-(2-bromo-4,5-dimethoxyphenyl)-3-(1-phenylvinyl)-2,5-dihydro)-pyrrole (4.12b)**.

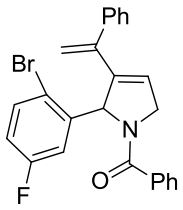
The treatment of enyne **4.9b** (0.072 g, 0.15 mmol, 1.0 equiv) with Grubb's I catalyst (0.012 g, 0.015 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded dihydropyrrole **4.12b** (0.058 g, 81%) as a yellow oil: R_f = 0.33 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 1H), 7.46-7.38 (m, 3H), 7.36-7.26 (m, 4H), 7.22 (t, *J* = 6.8 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.82 (s, 0.5H), 6.48 (s, 0.5H), 5.93 (s, 0.4H), 5.76 (s, 0.6H), 5.36 (s, 0.7H), 5.25 (s, 0.3H), 5.17 (s, 0.7H), 5.10 (s, 0.3H), 4.83- 4.65 (m, 1.5H), 4.28 (d, *J* = 24.4 Hz, 0.5H), 3.87 (s, 2H), 3.86 (s, 2H), 3.82 (s, 2H): The signals that integrate for less than ^{1}H arise due to hindered

rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (54.2), (55.9), 56.0, 56.1, 56.9, 67.9, 116.0, (116.9), 117.6, 124.7, 125.9, 127.2 (2C), 127.71 (2C), 127.76, 128.0, 128.2 (2C), 128.3 (2C), 128.4, 129.2, 130.2, (130.9), 136.2, 140.7, 142.2, 148.6, 149.0, 169.7; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1444, 1159, 1026; HRMS (ES^{+}): calcd for $C_{27}H_{25}BrNO_3$ $(M+H)^{+}$ 490.1018, found 490.1024.



***N*-benzoyl-(2-(2-bromo-5-fluorophenyl)-3-(1-phenylvinyl)-2,5-dihydro)-pyrrole (4.12c)**.

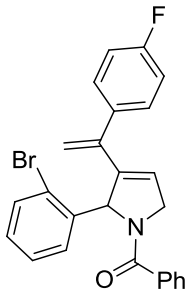
The treatment of enyne **4.9c** (0.094 g, 0.21 mmol, 1.0 equiv) with Grubb's I catalyst (0.018 g, 0.02 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded dihydropyrrole **4.12c** (0.068 g, 72%) as a colorless oil: R_f = 0.75 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.47 (m, 2H), 7.46-7.35 (m, 3H), 7.31 (t, *J* = 6.8 Hz, 3H), 7.24-7.14 (m, 2H), 7.09 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 0.75H), 6.87 (td, *J* = 8.4 Hz, *J* = 2.8 Hz, 1H), 6.74 (br s, 0.25H), 6.57 (s, 0.75H), 6.03

(s, 0.25H), 5.94 (s, 0.25H), 5.76 (s, 0.75H), 5.34 (s, 0.75H), 5.23 (s, 0.25H), 5.16 (s, 0.75H), 5.09 (s, 0.25H), 4.81- 4.63 (m, 1.25H), 4.26 (d, *J* = 16.0 Hz, 0.75H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (54.3), 56.7, 67.4, 116.5 (d, *J* = 22.3 Hz, 2C), 117.7, 125.3, (125.5), 125.9, (126.5), 127.2 (2C), 127.83, 127.89, 127.9, 128.25 (2C), 128.27 (d, *J* = 19.1 Hz, 2C), 128.6, (129.0), 129.4, 130.3, 134.6 (d, *J* = 7.6 Hz), 135.8, (136.6), (140.2), 140.5, (141.8), 142.0, 161.3 (d, *J* = 245.2 Hz), 169.6; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1641, 1465, 1400; HRMS (ES^{+}): calcd for $C_{25}H_{20}BrFNO$ $(M+H)^{+}$ 448.0712, found 448.0720.



***N*-benzoyl-(2-(2-bromophenyl)-3-(1-(4-fluorophenyl)vinyl)-2,5-dihydro)-pyrrole (4.12d)**.

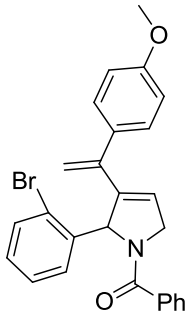
The treatment of enyne **4.9d** (0.079 g, 0.17 mmol, 1.0 equiv) with Grubb's I catalyst (0.015 g, 0.017 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:5)

afforded dihydropyrrole **4.12d** (0.069 g, 87%) as a colorless heavy oil: R_f = 0.47 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.49 (m, 2H), 7.47-7.36 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.68-7.10 (m, 5H), 7.02 (q, *J* = 8.8 Hz, 3H), 6.62 (s, 0.7H), 6.09 (s, 0.3H), 5.91 (s, 0.3H), 5.72 (s, 0.7H), 5.37 (s, 0.7H), 5.27 (s, 0.3H), 5.13 (s, 0.7H), 5.06 (s, 0.3H), 4.84-4.66 (m, 1.5H), 4.28 (d, *J* = 16.4 Hz, 0.5H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (54.3), 56.9, 67.6, 115.1 (d, *J* = 21.3 Hz, 2C), (117.0), 117.7, (124.0), 125.1, 125.9, 127.2 (2C), 127.7, 128.2 (2C), 128.5, 129.1, 129.2, [129.5, (d, *J* = 7.8 Hz,)], 129.5 (d, *J* = 8.0 Hz, 2C), 130.2, (132.6), 133.6, 136.1, (136.4), 136.7 (d, *J* = 3.1 Hz), (136.8), 139.4, 141.1, (141.2), (142.6), [162.4, (d, *J* = 245.5 Hz,)], 162.3 (d, *J* = 245.0 Hz), 169.6, (171.1); Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1508, 1448; HRMS (ES^+): calcd for $C_{25}H_{19}BrFNONa$ $(M+Na)^+$ 470.0532, found 470.0537.



***N*-benzoyl-(2-(2-bromophenyl)-3-(1-(4-fluorophenyl)vinyl)-2,5-dihydro)-pyrrole (4.12e)**.

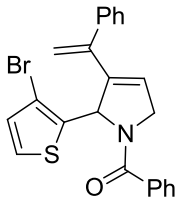
The treatment of enyne **4.9e** (0.09 g, 0.2 mmol, 1.0 equiv) with Grubb's I catalyst (0.016 g, 0.02 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (3:7) afforded dihydropyrrole **4.9e** (0.057 g, 63%) as colorless oil: R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 7.46-7.36 (m, 3H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2.5H), 7.18-7.09 (m, 1.5H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 9.2 Hz, 2H), 6.62 (br s, 0.7H), 6.09 (br s, 0.3H), 5.93 (s, 0.4H), 5.76 (s, 0.6H), 5.32 (s, 0.6H), 5.20 (br s, 0.4H), 5.12 (s, 0.6H), 5.05 (s, 0.4H), 4.82-4.68 (m, 1.4H), 4.28 (d, *J* = 16.0 Hz, 0.6H), 3.82 (s, 3H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.9a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (54.3), 55.2, 56.9, 67.6, 115.9, 116.7, (124.0), 124.8, 125.9, 127.2 (2C), 127.6, (127.8), (128.1), 128.2 (2C), 128.4, 129.0 (2C), 129.2, 129.3 (2C), (129.7), 130.1, (132.6), 132.9, 133.2, 133.5, 136.2, (136.8), (139.5),

141.60, (141.65), (142.9), 159.1, (159.2), 169.5, (171.2); Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1398, 1027; HRMS (ES^+): calcd for $C_{26}H_{23}BrNO_2$ $(M+H)^+$ 460.0912, found 460.0904.



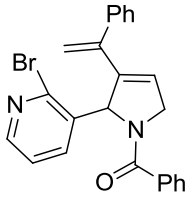
***N*-benzoyl-(2-(3-bromothiophen-2-yl)-3-(1-phenylvinyl)-2,5-dihydro)-pyrrole (4.12f)**.

The treatment of enyne **4.9k** (0.097 g, 0.22 mmol, 1.0 equiv) with Grubb's I catalyst (0.018 g, 0.22 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:8) afforded dihydropyrrole **4.12f** (0.079 g, 81%) as a colorless heavy oil: R_f = 0.59 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 6.4 Hz, 1H), 7.46-7.39 (m, 2H), 7.37-7.30 (m, 6H), 7.25 (d, *J* = 4.8 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 5.6 Hz, 0.7H), 6.73 (d, *J* = 3.6 Hz, 0.7H), 6.63 (d, *J* = 5.2 Hz, 0.3H), 6.11 (s, 0.3H), 5.87 (s, 0.3H), 5.71 (s, 0.7H), 5.39 (s, 0.7H), 5.28 (s, 0.3H), 5.23 (s, 0.7H), 5.14 (s, 0.3H), 4.78- 4.64 (m, 1.5H), 4.22 (d, *J* = 16.0 Hz, 0.5H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (53.3), 56.0, 61.9, (63.6), (110.7), 110.8, (116.8), 117.7, 124.7, (124.92), (124.99), (125.5), 125.8, (126.8), 127.3, 127.7, (127.8), (128.1), 128.22 (2C), 128.28 (2C), 128.3 (2C), (128.4), 128.7, (129.4), (129.5), 130.3 (2C), 135.8, (136.5), 138.9, (139.9), (140.5), 140.6, 141.8, (141.9), 142.2, (143.1), 169.4, (170.9); Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1577, 1446; HRMS (ES^+): calcd for $C_{23}H_{18}BrNOSNa$ $(M+Na)^+$ 458.0190, found 458.0181.



***N*-benzoyl-(2-(2-bromopyridin-3-yl)-3-(1-phenylvinyl)-2,5-dihydro)-pyrrole (4.12g)**.

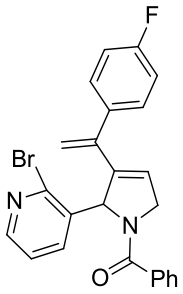
The treatment of enyne **4.9m** (0.072 g, 0.17 mmol, 1.0 equiv) with Grubb's I catalyst (0.014 g, 0.017 mmol, 0.1 equiv) according to the general procedure described above followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded dihydropyrrole **4.12g** (0.05 g, 69%) as a colorless oil: R_f = 0.55 (EtOAc/Hexane 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (ddd, *J* = 10.0 Hz, *J* = 6.0 Hz, *J* = 1.6 Hz, 0.7H), 8.19 (br s, 0.3H), 7.78 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 0.5H), 7.71 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 0.5H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.42 (q, *J* = 7.2 Hz, 3H), 7.38-7.30 (m, 4H), 7.23-7.29 (m, 1H), 7.20 (br s, 1H), 7.03 (br s, 0.5H), 6.49 (s, 0.5H), 6.15-5.90 (m, 0.3H),

5.83 (s, 0.7H), 5.34 (s, 0.5H), 5.28 (s, 0.5H), 5.19 (d, *J* = 4.0 Hz, 0.7H), 5.11 (d, *J* = 11.2 Hz, 0.3H), 4.82-4.67 (m, 1.3H), 4.31 (d, *J* = 16.4 Hz, 0.7H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (54.3), 57.1, (66.4), 67.8, 117.4, (117.7), (122.6), 122.9, (125.7), 125.81, (125.89), 127.2 (2C), 127.91, 127.96, 128.1 (2C), 128.2 (2C), 128.4 (2C), 128.7, 128.8, (129.7), 130.4, (134.2), 135.7, (136.5), (140.0), 140.2, 142.0, (142.1), 148.7, (148.8), 149.1, (150.2), 169.9; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1497, 1400; HRMS (ES^{+}): calcd for $C_{24}H_{20}BrN_2O$ $(M+H)^{+}$ 431.0759, found 431.0769.



***N*-benzoyl-(2-(2-bromopyridin-3-yl)-3-(1-(4-fluorophenyl)vinyl)-2,5-dihydro)-pyrrole (4.12h)**.

The treatment of enyne **4.9n** (0.066 g, 0.147 mmol, 1.0 equiv) with Grubbs I catalyst (0.012 g, 0.015 mmol, 0.1 equiv) according to the general procedure described above followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3)

afforded dihydropyrrole **4.12h** (0.039 g, 60%) as a colorless oil: R_f = 0.5 (EtOAc/Hexane 7:3).

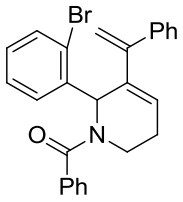
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (br s, 0.8H), 8.1 (br s, 0.2H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 6.4 Hz, 2H), 7.49-7.38 (m, 4H), 7.25-7.14 (m, 1H), 7.08-6.97 (m, 3.5H), 6.47 (s, 0.5H), 6.10-5.90 (m, 0.3H), 5.8 (s, 0.7H), 5.31 (s, 1H), 5.16 (s, 1H), 4.85-4.65 (m, 1.3H), 4.25 (d, *J* = 16.8 Hz, 0.7H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the diene **4.12a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 57.9, 67.8, 115.2 (d, *J* = 21.3 Hz, 2C), 117.8, 122.9, (125.2), 125.7, 126.0, 127.2 (2C), 128.2 (d, *J* = 6.3 Hz), 128.42 (2C), 128.48, (128.8), (129.5), 129.8 (d, *J* = 7.7 Hz, 2C), 130.1, 130.5, (133.5), 135.7, 136.2, 141.1, 149.2, 162.3 (d, *J* = 245.2 Hz), 170.0; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1465, 1409; HRMS (ES^+): calcd for $C_{24}H_{18}BrFN_2ONa$ $(M+Na)^+$ 471.0484, found 471.0481.

General procedure for the synthesis of dihydropyridines 4.13a-i:

The solution of 1,7-enynes **4.9f-j, 4.9l** or **4.9p-r** (1.0 equiv) in toluene (5-10 mL) was degassed with ethylene for 5 min, Grubb's II catalyst (0.1 equiv) was added, and the mixture was stirred at 85^{o}C under ethylene atmosphere for 8h. The mixture was cooled to rt, directly loaded on a silica column and purified by flash chromatography eluting with EtOAc/Hexane mixtures to afford dihydropyridines **4.13a-i**.



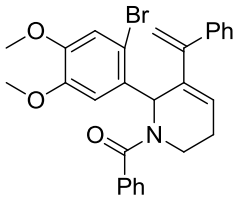
***N*-benzoyl-(2-(2-bromophenyl)-3-(1-phenylvinyl)-5,6-dihydropyridine (4.13a)**.

The treatment of enyne **4.9f** (0.12 g, 0.27 mmol, 1.0 equiv) with Grubb's II catalyst (0.023 g, 0.027 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:8) afforded dihydropyridine **4.13a** (0.108 g, 92%) as a colorless oil: R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 3H), 7.45-7.40 (m, 3H), 7.37-7.31 (m, 6H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.97 (br s, 1H), 5.98 (br s, 1H), 5.15 (br s, 1H), 5.04 (br s, 1H), 3.57 (br s, 1H), 3.16 (br s, 1H), 2.26 (br s, 1H), 2.11 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 40.1, 52.9, 115.1, 125.1, 126.8, 127.3, 127.5, 127.7, 128.0 (2C), 128.4, 128.9 (2C), 129.3, 129.9 (2C), 131.0, 133.8 (2C), 135.8, 137.1, 138.6, 141.1, 147.0, 171.3.

IR (cm^{-1}) 1645, 1465, 1409; HRMS (ES^+): calcd for $C_{26}H_{23}BrNO$ $(M+H)^+$ 444.0963, found 444.0964.



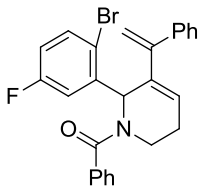
***N*-benzoyl-(2-(2-bromo-4,5-dimethoxyphenyl)-3-(1-phenylvinyl)-5,6-dihydropyridine (4.13b)**.

The treatment of enyne **4.9g** (0.055 g, 0.11 mmol, 1.0 equiv) with Grubb's II catalyst (0.0093 g, 0.011 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded dihydropyridine **4.13b** (0.048 g, 87%) as a colorless heavy oil: R_f = 0.4 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.49 (m, 3H), 7.48-7.28 (m, 7H), 7.16 (br s, 1H), 7.02 (s, 1H), 6.88 (br s, 1H), 6.00 (br s, 1H), 5.20 (br s, 1H), 5.06 (br s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.61 (br s, 1H), 3.21 (br s, 1H), 2.28 (br s, 1H), 2.11 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 40.2, 52.8, 56.18, 56.19, 114.1, 115.3, 116.4, 127.4, 127.5, 127.9, 128.1 (2C), 128.3, 128.6, 128.8 (2C), 129.9 (2C), 130.6, 135.9, 137.5, 141.0, 146.9, 147.6 (2C), 149.0, 171.1.

IR (cm^{-1}) 1643, 1440, 1205, 1026; HRMS (ES^+): calcd for $C_{28}H_{26}BrNO_3Na$ $(M+Na)^+$ 526.0994, found 526.0994.



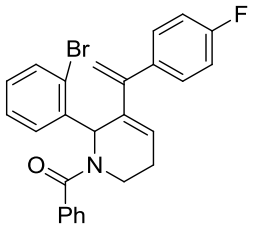
***N*-benzoyl-(2-(2-bromo-5-fluorophenyl)-3-(1-phenylvinyl)-5,6-dihydropyridine (4.13c)**.

The treatment of enyne **4.9h** (0.09 g, 0.19 mmol, 1.0 equiv) with Grubb's II catalyst (0.016 g, 0.019 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded dihydropyridine **4.13c** (0.079 g, 88%) as a yellow heavy oil: R_f = 0.55 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 7.48-7.52 (m, 2H), 7.45-7.35 (m, 6H), 7.34-7.30 (m, 2H), 7.24 (dd, *J* = 9.6 Hz, *J* = 2.8 Hz, 1H), 7.10-6.75 (m, 2H), 6.01 (br s, 1H), 5.13 (br s, 1H), 5.06 (br s, 1H), 3.60 (br s, 1H), 3.14 (br s, 1H), 2.25 (br s, 1H), 2.11 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 40.2, 52.7, 115.2, 116.8, [117.7, (d, *J* = 22.1 Hz)], 118.2 (d, *J* = 24.0 Hz), (119.1), 126.8, 127.4 (d, *J* = 12.0 Hz, 2C), 128.1 (2C), 128.4, 128.81, 128.88 (2C), (129.3), 129.9, 130.1, 130.4, 133.8, 134.9 (d, *J* = 7.6 Hz, 2C), (135.6), 136.7, 140.8, 146.9, 161.6 (d, *J* = 245.1 Hz), [161.9, (d, *J* = 246.7 Hz)], (171.4), 172.6; Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1649, 1465, 1445; HRMS (ES^+): calcd for $C_{26}H_{22}BrFNO$ $(M+H)^+$ 462.0869, found 462.0862.



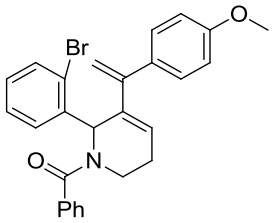
***N*-benzoyl-(2-(2-bromophenyl)-3-(1-(4-fluorophenyl)vinyl)-5,6-dihydropyridine (4.13d)**.

The treatment of enyne **4.9i** (0.08 g, 0.17 mmol, 1.0 equiv) with Grubb's II catalyst (0.015 g, 0.017 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded dihydropyridine **4.13d** (0.068 g, 85%) as a colorless oil: R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.62-7.47 (m, 4H), 7.44-7.38 (m, 3H), 7.36-7.30 (m, 2H), 7.24-7.30 (m, 1H), 7.05 (t, *J* = 8.4 Hz, 2H), 6.93 (br s, 1H), 5.98 (br s, 1H), 5.15 (br s, 1H), 5.02 (br s, 1H), 3.60 (br s, 1H), 3.17 (br s, 1H), 2.28 (br s, 1H), 2.12 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 40.1, 53.0, 114.9 (d, *J* = 21.2 Hz, 2C), 115.4, 125.1, 126.8, 127.5, 128.4, 128.9, 129.4, 130.0 (2C), 130.4 (d, *J* = 7.8 Hz, 2C), 130.9, 133.9 (2C), 135.8, 136.9 (d, *J* = 3.3 Hz), 137.3, 138.5, 146.1, 160.2 (d, *J* = 244.5 Hz), 171.3.

IR (cm^{-1}) 1643, 1440, 1402; HRMS (ES^+): calcd for $C_{26}H_{21}BrFNONa$ $(M+Na)^+$ 484.0688, found 484.0688.



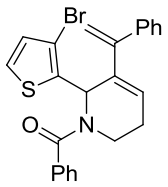
***N*-benzoyl-(2-(2-bromophenyl)-3-(1-(4-methoxyphenyl)vinyl)-5,6-dihydropyridine (4.13e)**.

The treatment of enyne **4.9j** (0.079 g, 0.17 mmol, 1.0 equiv) with Grubb's II catalyst (0.014 g, 0.017 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:8) afforded dihydropyridine **4.13e** (0.063 g, 80%) as a colorless oil: R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.50 (d, *J* = 6.4 Hz, 3H), 7.46-7.37 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.30-7.17 (m, 3H), 6.94 (br s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.03 (br s, 1H), 5.11 (br s, 1H), 5.02 (br s, 1H), 3.84 (s, 3H), 3.56 (br s, 1H), 3.16 (br s, 1H), 2.27 (br s, 1H), 2.11 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 39.1, 52.0, 54.3, 112.3 (2C), 113.3, 124.3, 125.7, 126.5, 127.3, 127.6, 128.2, 128.90 (2C), 128.93 (2C), 130.0, 132.3, 132.8 (2C), 134.8, 136.4, 137.6, 145.6, 157.8, 170.3.

IR (cm^{-1}) 1639, 1485, 1446; HRMS (ES^+): calcd for $C_{27}H_{25}BrNO_2$ $(M+H)^+$ 474.1069, found 474.1069.



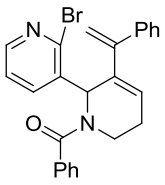
***N*-benzoyl-2-(3-bromothiophen-2-yl)-3-(1-phenylvinyl)-5,6-dihydropyridine (4.13f).**

The treatment of enyne **18b** (0.17 g, 0.38 mmol, 1.0 equiv) with Grubb's II catalyst (0.032 g, 0.038 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded dihydropyridine **4.9l** (0.14 g, 82%) as a colorless oil: R_f = 0.55 (EtOAc/Hexane 1:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.46 (br, 2H), 7.42 (t, *J* = 7.2 Hz, 3H), 7.40-7.30 (m, 5H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.09 (br, 1H), 7.03 (br, 1H), 5.89 (br, 1H), 5.37 (br, 1H), 5.13 (br, 1H), 3.69 (br, 1H), 3.52 (br, 1H), 2.32 (br, 1H), 2.18 (br, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 40.2, 47.8, 111.1, 115.0, 125.3, 127.1, 127.4, 128.0 (2C), 128.4 (2C), 128.6, 128.7 (2C), 129.8 (2C), 130.9, 135.8, 137.8, 138.3, 141.1, 146.7, 170.2.

IR (cm^{-1}) 1640, 1431, 1447; HRMS (ES^+): calcd for $C_{24}H_{20}BrNOSNa$ $(M+Na)^+$ 472.0347, found 472.0343.



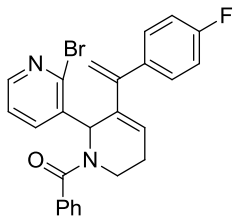
***N*-benzoyl-(2'-bromo-3-(1-phenylvinyl)-5,6-dihydro-[2,3'-bipyridine] (4.13p)**.

The treatment of enyne **4.9p** (0.065 g, 0.15 mmol, 1.0 equiv) with Grubb's II catalyst (0.012 g, 0.015 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded dihydropyridine **4.13p** (0.045 g, 69%) as a colorless heavy oil: R_f = 0.3 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.47-7.30 (m, 9H), 6.92 (s, 1H), 6.05 (s, 1H), 5.14 (s, 1H), 5.07 (s, 1H), 3.63 (br s, 1H), 3.05 (br s, 1H), 2.27 (br s, 1H), 2.11 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 40.2, 52.3, 115.4, 122.2, 127.5 (2C), 127.7, 128.1 (2C), 128.4, 128.7 (2C), 129.5, 130.2 (2C), 135.5, 136.0, 136.2, 139.1, 140.6, 144.8, 146.8, 149.1, 171.7.

IR (cm^{-1}) 1643, 1446, 1402; HRMS (ES^+): calcd for $C_{25}H_{21}BrN_2ONa$ $(M+Na)^+$ 467.0735, found 467.0742.

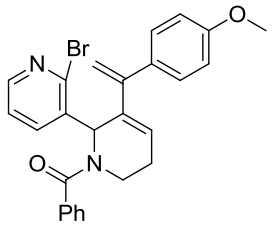


***N*-benzoyl-(2'-bromo-3-(1-(4-fluorophenyl)vinyl)-5,6-dihydro-[2,3'-bipyridine] (4.13q)**.

The treatment of enyne **4.9q** (0.1 g, 0.22 mmol, 1.0 equiv) with Grubb's II catalyst (0.019 g, 0.022 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded dihydropyridine **4.13q** (0.062 g, 62%) as a colorless oil: R_f = 0.35 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.74 (dd, *J* = 7.2 Hz, *J* = 1.6 Hz, 1H), 7.52 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 2H), 7.47-7.39 (m, 3H), 7.32 (dd, *J* = 4.8 Hz, *J* = 2.8 Hz, 1H), 7.30-7.22 (m, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 6.86 (br s, 1H), 6.08 (s, 1H), 5.13 (br s, 1H), 5.05 (s, 1H), 3.64 (br s, 1H), 3.05 (br s, 1H), 2.31 (br s, 1H), 2.14 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 40.2, 52.4, 115.1 (d, *J* = 21.2 Hz, 2C), 115.66, 115.68, 122.1, 127.5 (2C), 128.5, 129.5, 130.2 (2C), 130.3 (d, *J* = 8.0 Hz, 2C), 135.4, 135.8, 136.4 (d, *J* = 3.2 Hz), 139.0, 144.8, 146.0, 149.2, 162.3 (d, *J* = 245 Hz), 171.7. IR (cm^{-1}) 1645, 1508, 1402; HRMS (ES^+): calcd for $C_{25}H_{20}BrFN_2ONa$ $(M+Na)^+$ 485.0641, found 485.0634.



***N*-benzoyl-(2'-bromo-3-(1-(4-methoxyphenyl)vinyl)-5,6-dihydro-[2,3'-bipyridine] (4.13r)**.

The treatment of enyne **4.9r** (0.1 g, 0.21 mmol, 1.0 equiv) with Grubb's II catalyst (0.018 g, 0.021 mmol, 0.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded dihydropyridine **4.13r** (0.058 g, 58%) as a colorless oil: R_f = 0.3 (EtOAc/Hexane 3:7).

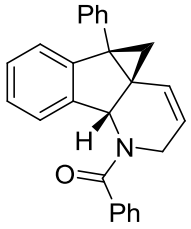
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 3.6 Hz, 1H), 7.75 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.53 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 2H), 7.48-7.39 (m, 3H), 7.30 (dd, *J* = 4.8 Hz, *J* = 2.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.94-6.88 (m, 2H), 6.87 (br s, 1H), 6.10 (s, 1H), 5.09 (br s, 1H), 5.04 (s, 1H), 3.85 (s, 3H), 3.64 (br s, 1H), 3.04 (br s, 1H), 2.31 (br s, 1H), 2.10 (br s, 1H); The broadening of some signals arise due to hindered rotation as suggested by the temperature dependent ^{1}H NMR recorded for the diene **4.13a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 40.3, 52.5, 55.1, 113.5 (2C), 114.8, 122.1, 127.5, 128.4 (2C), 129.1, 129.8 (2C), 130.1 (2C), 132.8, 135.5, 136.0, 136.6, 139.1, 144.8, 146.5, 149.1, 159.1, 171.7.

IR (cm^{-1}) 1647, 1458, 1400; HRMS (ES^+): calcd for $C_{26}H_{24}BrN_2O_2$ $(M+H)^+$ 475.1021, found 475.1018.

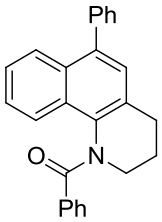
General procedure for the preparation of indenopyridines 4.21a-e and **tetrahydrophenanthroline 4.23a-c:**

To a mixture of solid $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv) and Cs_2CO_3 (2.0 equiv) in a sealed tube under argon was added a solution of dienes **4.13a-e** and **4.13g-i** (1.0 equiv) in DMF (2.0 mL). The tube was flushed with argon, capped and the reaction mixture was stirred at 120^{o}C for 15 h. The mixture was cooled to rt, water (2 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). Combined organic layers were washed with brine, dried (anhydrous $MgSO_4$) and solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over silica to afford indenopyridines **4.21a-e** and tetrahydrophenanthroline **4.23a-c**.



4.21a

and



4.20

(±) *N*-benzoyl-(4a*S*,5a*S*,9b*R*)-5a-phenyl-2,5,5a,9b-tetrahydro-cyclopropa[2,3]indeno[1,2-b]pyridine (4.21a) and ***N*-benzoyl-(6-phenyl-3,4-dihydrobenzo[h]quinoline (4.20)**.

The treatment of diene **4.13a** (0.1 g, 0.23 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.005 g, 0.023 mmol, 0.1 equiv), Cs_2CO_3 (0.147 g, 0.45 mmol, 2.0 equiv) and PPh_3 (0.012 g, 0.045 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:8) afforded indenopyridine **4.21a** (0.066 g, 80%) as a fluffy white solid and continuous elution with EtOAc/Hexane (1:8) afforded benzoquinoline **4.20** (0.008 g, 10%) as a white solid.

Analytical data for 4.21a: mp 73-78^{o}C; R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.2 Hz, 1H), 7.52-7.42 (m, 5H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.30-7.22 (m, 4H), 7.20 (t, *J* = 6.8 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.09-6.01 (m, 2H), 5.47 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 4.16-3.95 (m, 1H), 3.59 (d, *J* = 15.6 Hz, 1H), 2.31 (d, *J* = 5.6 Hz, 1H), 1.46 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 40.1, 43.1, 46.5, 59.6, 123.6, 126.8 (2C), 126.9, 127.0, 127.1, 127.9, 128.4 (2C), 128.5 (2C), 129.2, 129.6, 129.7 (2C), 131.2, 136.5, 138.5, 142.8, 149.0, 170.5.

IR (cm^{-1}) 1627, 1600, 1444; HRMS (ES^{+}): calcd for $C_{26}H_{21}NONa$ $(M+Na)^{+}$ 386.1521, found 386.1519.

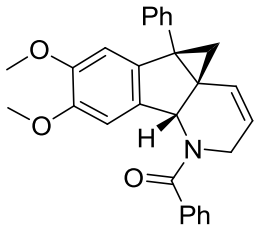
Analytical data for 4.20: mp 169-171^{o}C; R_f = 0.5 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.80 (br m, 1.7H), 7.69-7.62 (m, 2.3H), 7.56-7.41 (m, 7H), 7.24-7.19 (m, 2H), 7.06 (t, *J* = 6.8 Hz, 0.7H), 6.98 (t, *J* = 7.2 Hz, 1.3H), 5.06-4.82 (m, 0.5H), 4.36-4.12 (m, 0.5H), 3.62-3.51 (br m, 0.4H), 3.43-3.33 (br m, 0.6H), 3.16-3.01 (m, 1H), 2.86-2.68 (m, 1H), 2.53-2.41 (br m, 0.5H), 2.15-1.98 (br m,

0.5H), 1.87-1.69 (br m, 1H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the phenanthroline **4.23a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (24.8), 24.9, (25.3), 25.9, 43.1, (47.8), 122.6, (123.1), (125.5), (125.6), 125.7, 126.2, 126.8, (127.1), 127.30, (127.35), 127.4 (2C), (127.5), 127.6, (127.8), 128.02 (2C), (128.07), (128.2), (128.3), 128.3 (2C), 128.6, (129.4), 129.6 (2C), (129.9), 130.0, (130.1), 130.8, (130.9), (132.0), 132.2, 132.3, (136.0), 136.5, (136.7), 138.9, (139.6), 140.3, (140.9), 170.3, (172.6); Signals for the minor rotamer are given in the parentheses.

IR (cm^{-1}) 1641, 1490, 1467; HRMS (ES^{+}): calcd for $C_{26}H_{22}NO$ $(M+H)^{+}$ 364.1701, found 364.1696.



(±) *N*-benzoyl-(4a*S*,5a*S*,9b*R*)-7,8-dimethoxy-5a-phenyl-2,5,5a,9b-tetrahydro-cyclopropa[2,3]indeno[1,2-b]pyridine (4.21b).

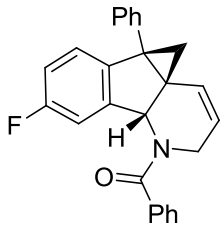
The treatment of diene **4.13b** (0.04 g, 0.08 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0018 g, 0.008 mmol, 0.1 equiv), Cs_2CO_3 (0.058 g, 0.16 mmol, 2.0 equiv) and PPh_3 (0.0042 g, 0.016 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4)

afforded indenopyridine **4.13b** (0.026 g, 78%) as a light yellow solid: mp 220-222^{o}C; R_f = 0.35 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.43 (m, 5H), 7.39-7.32 (m, 2H), 7.31-7.23 (m, 4H), 6.48 (s, 1H), 6.03-5.96 (m, 2H), 5.44 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 4.08-3.98 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.61 (d, *J* = 15.6 Hz, 1H), 2.29 (d, *J* = 5.6 Hz, 1H), 1.40 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 40.0, 43.1, 46.3, 56.0, 56.1, 59.7, 106.3, 109.4, 126.80, 126.84 (2C), 128.4 (2C), 128.5 (2C), 129.1, 129.4 (2C), 129.6, 131.3, 134.1, 136.5, 138.6, 140.9, 148.7, 149.2, 170.4.

IR (cm^{-1}) 1625, 1423, 1130, 1116; HRMS (ES^{+}): calcd for $C_{28}H_{26}NO_3$ $(M+H)^{+}$ 424.1913, found 424.1913.



(±) *N*-benzoyl-(4a*S*,5a*S*,9b*R*)-8-fluoro-5a-phenyl-2,5,5a,9b-tetrahydro-cyclopropa[2,3]indeno[1,2-b]pyridine (4.21c).

The treatment of diene **4.13c** (0.06 g, 0.13 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.003 g, 0.013 mmol, 0.1 equiv), Cs_2CO_3 (0.085 g, 0.26 mmol, 2.0 equiv) and PPh_3 (0.0068 g, 0.026 mmol, 0.2 equiv) according to the general procedure described above, followed

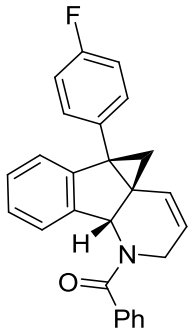
by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded indenopyridine **4.21c** (0.034 g, 71%) as a colorless heavy oil:

R_f = 0.5 (EtOAc/Hexane 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.40 (m, 6H), 7.32-7.28 (m, 2H), 7.30-7.21 (m, 3H), 6.90 (d, *J* = 6.4 Hz, 2H), 6.09-5.97 (m, 2H), 5.45 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 4.13-4.01 (m, 1H), 3.60 (d, *J* = 16.0 Hz, 1H), 2.29 (d, *J* = 5.6 Hz, 1H), 1.44 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 40.3, 43.2, 45.7, 59.3, 113.5 (d, *J* = 22.5 Hz), 115.1 (d, *J* = 23.0 Hz), 124.5 (d, *J* = 9.0 Hz), 126.8 (2C), 127.0, 128.4 (2C), 128.5 (2C), 129.1, 129.6 (2C), 129.7, 131.0, 136.2, 138.3, 144.5 (d, *J* = 2.7 Hz), 144.9 (d, *J* = 8.1 Hz), 162.1 (d, *J* = 242.8.1 Hz), 170.5.

IR (cm^{-1}) 1625, 1600, 1483; HRMS (ES^+): calcd for $C_{26}H_{21}NFO$ $(M+H)^+$ 382.1607, found 382.1599.



(±) *N*-benzoyl-(4a*S*,5a*S*,9b*R*)-5a-(4-fluorophenyl)-2,5,5a,9b-tetrahydro-cyclopropa[2,3]indeno[1,2-b]pyridine (4.21d).

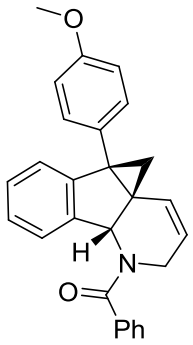
The treatment of diene **4.13d** (0.06 g, 0.13 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.003 g, 0.013 mmol, 0.1 equiv), Cs_2CO_3 (0.084 g, 0.26 mmol, 2.0 equiv) and PPh_3 (0.007 g, 0.026 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded indenopyridine **4.21d** (0.04 g, 81%) as a colorless oil:

R_f = 0.55 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.2 Hz, 1H), 7.54-7.41 (m, 5H), 7.26-7.18 (m, 4H), 7.03 (t, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.10-5.99 (m, 2H), 5.45 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 4.13-4.01 (m, 1H), 3.56 (d, *J* = 15.6 Hz, 1H), 2.25 (d, *J* = 5.6 Hz, 1H), 1.46 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 40.0, 43.0, 45.7, 59.5, 115.3 (d, *J* = 21.2 Hz, 2C), 123.4, 126.8 (2C), 127.1, 127.2, 128.0, 128.5 (2C), 129.3, 129.6, 131.1, 131.2 (d, *J* = 8.1 Hz, 2C), 134.3 (d, *J* = 3.1 Hz), 136.4, 142.7, 148.8, 161.4 (d, *J* = 244.1 Hz), 170.5.

IR (cm^{-1}) 1625, 1598, 1427; HRMS (ES^+): calcd for $C_{26}H_{20}FNONa$ $(M+Na)^+$ 404.1427, found 404.1419.



(±) *N*-benzoyl-(4a*S*,5a*S*,9b*R*)-5a-(4-methoxyphenyl)-2,5,5a,9b-tetrahydro-cyclopropa[2,3]indeno[1,2-b]pyridine (4.21e).

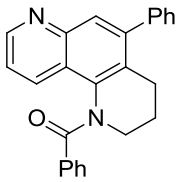
The treatment of diene **4.13e** (0.038 g, 0.08 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.002 g, 0.008 mmol, 0.1 equiv), Cs_2CO_3 (0.052 g, 0.16 mmol, 2.0 equiv) and PPh_3 (0.0042 g, 0.016 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:8) afforded indenopyridine **4.21e** (0.025 g, 80%) as a colorless oil:

R_f = 0.4 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 6.8 Hz, 1H), 7.52-7.42 (m, 5H), 7.26-7.15 (m, 4H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.09-5.99 (m, 2H), 5.48 (dd, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 4.12-4.00 (m, 1H), 3.82 (s, 3H), 3.58 (d, *J* = 15.2 Hz, 1H), 2.24 (d, *J* = 5.6 Hz, 1H), 1.40 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 39.9, 43.0, 45.9, 55.2, 59.5, 113.8 (2C), 123.5, 126.9 (2C), 127.0, 127.1, 127.9, 128.5 (2C), 129.0, 129.5, 130.6, 130.8 (2C), 131.5, 136.6, 142.6, 149.3, 158.5, 170.5.

IR (cm^{-1}) 1625, 1598, 1245; HRMS (ES^+): calcd for $C_{27}H_{23}NO_2Na$ $(M+Na)^+$ 416.1626, found 416.1626.



***N*-benzoyl-(5-phenyl-2,3,4-trihydro)-1,7-phenanthroline (4.23a)**.

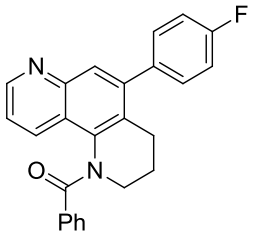
The treatment of diene **4.13g** (0.04 g, 0.09 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.002 g, 0.01 mmol, 0.1 equiv), Cs_2CO_3 (0.059 g, 0.18 mmol, 2.0 equiv) and PPh_3 (0.0065 g, 0.02 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded phenanthroline **4.23a** (0.022 g, 65%) as a light yellow powder: mp 190-193^oC; R_f = 0.3 (EtOAc/Hexane 3:7).

^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 0.2H), 8.68 (br s, 0.3H), 8.15 (d, *J* = 6.4 Hz, 0.3H), 8.05-7.90 (m, 1.5H), 7.82 (d, *J* = 5.2 Hz, 0.7H), 7.65-7.38 (m, 7H), 7.32-7.24 (m, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 6.8 Hz, 1H), 4.86 (q, *J* = 8.4 Hz, 0.5H), 4.25 (br s, 0.5H), 3.57 (br s, 0.5H), 3.42 (br s, 0.5H), 3.14 (d, *J* = 15.2 Hz, 0.5H), 2.93-2.70 (m, 1.5H), 2.47 (br s, 0.5H), 2.06 (br s, 0.5H), 1.81 (br s, 1H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^1H NMR recorded for the phenanthroline **4.23a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (24.9), 25.0, (25.8), 43.5, (47.9), 53.4, 120.3, (120.8), 122.8, (122.9), (127.5), 127.7 (2C), (127.8), 127.9, 128.1 (2C), (128.2), (128.3), 128.4 (2C), 128.8, (129.2), 129.5 (2C), 130.3, 131.0, (131.1), (132.1), 132.5, (135.1),

(135.5), 136.0, 136.4, 139.6, (140.1), 142.6, (143.5), 146.7, 150.0, (170.2), 172.9; Signals for the minor rotamer are given in the parentheses.

IR (cm^{-1}) 1643, 1444, 1394; HRMS (ES^+): calcd for $C_{25}H_{20}N_2ONa$ $(M+Na)^+$ 387.1473, found 387.1475.



***N*-benzoyl-(5-(4-fluorophenyl)-2,3,4-trihydro)-1,7-phenanthroline (4.23b)**.

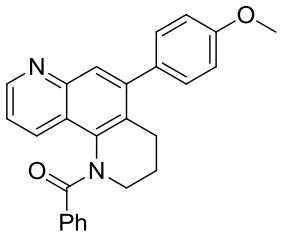
The treatment of diene **4.13h** (0.055 g, 0.12 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0027 g, 0.012 mmol, 0.1 equiv), Cs_2CO_3 (0.078 g, 0.24 mmol, 2.0 equiv) and PPh_3 (0.0063 g, 0.024 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded phenanthroline **4.23b** (0.03 g, 61%) as a colorless oil: R_f = 0.3 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (br s, 0.25H), 8.67 (br s, 0.25H), 8.15 (d, *J* = 6.8 Hz, 0.25H), 7.91 (d, *J* = 8.8 Hz, 1.5H), 7.82 (d, *J* = 6.0 Hz, 0.75H), 7.62-7.52 (m, 1.25H), 7.51-7.35 (m, 2.75H), 7.25-7.15 (m, 4H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 4.94-4.80 (m, 0.5H), 4.30-3.05 (m, 0.5H), 3.72-3.72 (m, 0.5H), 3.42 (br s, 0.5H), 3.09 (d, *J* = 14.0 Hz, 0.5H), 2.85-2.70 (m, 1.5H), 2.48 (br, 0.5H), 2.12-2.00 (m, 0.5H), 1.92-1.73 (m, 1H); The signals that integrate for less than 1H arise due to

hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the phenanthroline **4.23a**.

^{13}C NMR (125 MHz, $CDCl_3$) δ (24.9), 25.0, (25.8), 43.4, 47.9, (53.4), 115.2, 115.5 (d, *J* = 21.3 Hz, 2C), [115.5 (d, *J* = 21.3 Hz,)], 120.4, (121.0), (122.9), 126.8, 127.7 (2C), (128.0), 128.1 (2C), 128.2, (128.5), (128.6), 128.8, (129.3), (129.9), (130.2), 130.3 (d, *J* = 5.0 Hz), [130.8 (d, *J* = 7.6 Hz,)], 130.9, 131.1 (d, *J* = 7.5 Hz, 2C), [131.4 (d, *J* = 8.2 Hz,)], 131.9, (132.3), (135.4), (135.6), 135.9, (136.6), 141.4, (142.3), 146.7, (149.5), 150.2, 162.5 (d, *J* = 247 Hz), 170.2, (172.9); Signals for the minor rotamer are given in parentheses.

IR (cm^{-1}) 1643, 1467, 1402; HRMS (ES^{+}): calcd for $C_{25}H_{20}FN_2O$ $(M+H)^{+}$ 383.1560, found 383.1547.



***N*-benzoyl-(5-(4-methoxyphenyl)-2,3,4-trihydro)-1,7-phenanthroline (4.23c)**.

The treatment of diene **4.13i** (0.08 g, 0.169 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0038 g, 0.017 mmol, 0.1 equiv), Cs_2CO_3 (0.11 g, 0.338 mmol, 2.0 equiv) and PPh_3 (0.009 g, 0.038 mmol, 0.2 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded phenanthroline **4.23c** (0.04 g, 59%) as a colorless oil: R_f = 0.25

(EtOAc/Hexane 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (br s, 0.25H), 8.66 (br s, 0.5H), 8.11 (d, *J* = 6.1 Hz, 0.25H), 7.93 (d, *J* = 8.4 Hz, 1.5H), 7.82 (d, *J* = 5.2 Hz, 0.5H), 7.57 (s, 1.25H), 7.49-7.33 (m, 3H), 7.21 (d, *J* = 7.2 Hz, 1.25H), 7.13-6.96 (m, 4.5H), 4.91-4.78 (m, 0.5H), 4.27-3.99 (m, 0.5H), 3.92 (s, 2H), 3.90 (s, 1H), 3.70-3.52 (m, 0.5H), 3.41 (br s, 0.5H), 3.17 (d, *J* = 15.6 Hz, 0.5H), 2.93-2.70 (m, 1.5H), 2.47 (br, 0.5H), 2.06 (br s, 0.5H), 1.92-1.75 (m, 1H); The signals that integrate for less than 1H arise due to hindered rotation as confirmed by the temperature dependent ^{1}H NMR recorded for the phenanthroline **4.23a**.

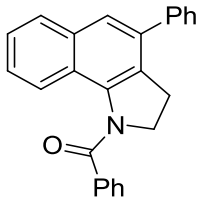
^{13}C NMR (125 MHz, $CDCl_3$) δ (25.0), 25.1, (25.8), 43.5, 47.9, (53.4), (55.3), 55.4, (113.7), 113.9 (2C), 120.2, (120.7), 122.7, (122.8), (126.8), 127.73 (2C), (127.76), 128.1 (2C), (128.2), (128.3), 128.6, 128.8, (130.3), 130.4, 130.7 (2C), 130.9, (131.1), 131.9, (132.5), 132.7, (135.0), (135.5), 136.0, 136.4, 142.2, (143.1), (146.8), 149.9, (159.0), 159.3, 170.2, (172.9); Signals for the minor rotamer is given in the parentheses.

IR (cm^{-1}) 1637, 1402, 1027; HRMS (ES^{+}): calcd for $C_{26}H_{23}N_2O_2$ $(M+H)^{+}$ 395.1760, found 395.1763.

General procedure for the synthesis of benzoindolines 4.22a-e, **thiopheno indoline 4.24** and **pyrroloquinoline 4.25a-b**:

A solution of the dienes **4.12a-h** in DMF (2 mL) was added a mixture of solid $Pd(OAc)_2$ (0.1 equiv) and NaOAc (1.1 equiv) in a sealed tube. The tube was flushed with argon, capped, and the reaction mixture was stirred at 120^{o}C for 12h. The

mixture was cooled to rt, cold water (2 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). Combined organic layers were washed with brine, dried (anhydrous $MgSO_4$), solvents were removed under reduced pressure to afford the crude products that were purified by flash chromatography over silica eluting with EtOAc/Hexane mixture to afford heterocycles benzoindolines **4.22a-e** and pyrroloquinoline **4.25a-b**.



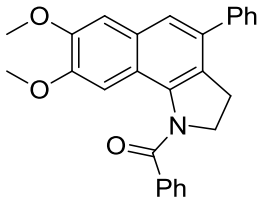
***N*-benzoyl-4-phenyl-2,3-dihydro-benzo[g]indole (4.22a)**.

The treatment of diene **4.12a** (0.048 g, 0.11 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0026 g, 0.01 mmol, 0.1 equiv) and NaOAc (0.01 g, 0.12 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded benzoindoline **4.22a** (0.028 g, 71%) as a white solid: mp 178-180^{o}C; R_f = 0.6 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.82 (m, 3H), 7.81-7.76 (m, 1H), 7.74 (s, 1H), 7.58-7.35 (m, 9H), 7.43-7.38 (m, 1H), 4.29 (t, *J* = 7.6 Hz, 2H), 3.22 (t, *J* = 7.6 Hz, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 55.1, 123.8, 125.2, 125.5, 125.7 126.4, 127.4, 128.3, 128.52 (2C), 128.54 (2C), 128.56 (2C), 128.9(2C), 130.3, 131.5, 133.9, 135.9, 136.5, 139.5, 140.2, 170.8.

IR (cm^{-1}) 1650, 1494, 1386; HRMS (ES^+): calcd for $C_{25}H_{19}NONa$ $(M+Na)^+$ 372.1364, found 372.1375.



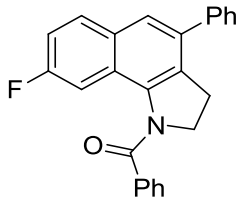
***N*-benzoyl-(7,8-dimethoxy-4-phenyl-2,3-dihydro-benzo[g]indole (4.22b)**.

The treatment of diene **4.12b** (0.035 g, 0.07 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0016 g, 0.007 mmol, 0.1 equiv) and NaOAc (0.0063 g, 0.077 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:3) afforded benzoindoline **4.22b** (0.02 g, 68%) as a yellow oil: R_f = 0.23 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.8 Hz, 2H), 7.60 (s, 1H), 7.57-7.45 (m, 7H), 7.39 (t, *J* = 6.8 Hz, 1H), 7.18 (s, 1H), 7.02 (s, 1H), 4.28 (t, *J* = 7.2 Hz, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.21 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.6, 55.2, 55.8, 55.9, 104.3 106.6, 119.6, 124.8, 127.1, 128.4 (2C), 128.5 (2C), 128.6, 128.7 (2C), 130.0, 131.31, 131.35 (2C), 134.7, 136.3, 138.3, 140.4, 149.0, 149.9, 170.2.

IR (cm^{-1}) 1649, 1498, 1161, 1012; HRMS (ES^+): calcd for $C_{27}H_{24}O_3N$ $(M+H)^+$ 410.1756, found 410.1756.



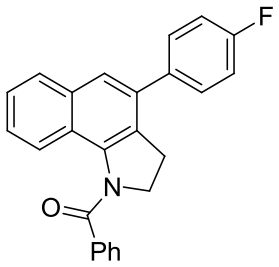
***N*-benzoyl-(8-fluoro-4-phenyl-2,3-dihydro-benzo[g]indole (4.22c)**.

The treatment of diene **4.12c** (0.029 g, 0.065 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0015 g, 0.006 mmol, 0.1 equiv) and NaOAc (0.006 g, 0.07 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded benzoindoline **4.22c** (0.016 g, 65%) as a heavy oil: R_f = 0.72 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.82 (m, 3H), 7.75 (s, 1H), 7.64-7.38 (m, 8H), 7.28 (d, *J* = 1.2 Hz, 2H), 4.30 (t, *J* = 6.4 Hz, 2H), 3.23 (t, *J* = 6.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 55.0, 109.2 (d, *J* = 23.0 Hz), 116.3 (d, *J* = 25.2 Hz), 124.8 (d, *J* = 9.9 Hz), 126.3, 127.5 (2C), 128.5 (2C), 128.6 (2C), 128.8 (2C), 130.7, 130.8, 131.0, 131.5, 131.6, 135.7, 135.8 (d, *J* = 2.7 Hz), 139.3 (d, *J* = 5.4 Hz), 139.9, 160.1 (d, *J* = 245.1 Hz), 170.7.

IR (cm^{-1}) 1650, 1496, 1357; HRMS (ES^+): calcd for $C_{25}H_{19}FNO$ $(M+H)^+$ 368.1451, found 368.1446.



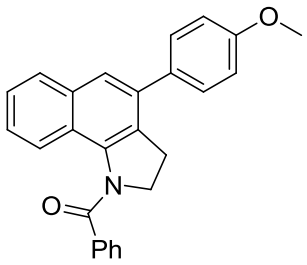
***N*-benzoyl-4-fluorophenyl-2,3-dihydro-benzo[g]indole (4.22d)**.

The treatment of diene **4.12d** (0.038 g, 0.085 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.002 g, 0.008 mmol, 0.1 equiv) and NaOAc (0.0078 g, 0.094 mmol, 1.1 equiv) according to the general procedure described above, followedby flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded benzoindoline **4.22d** (0.024 g, 78%) as a heavy oil: R_f = 0.75 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.87 (m, 3H), 7.81 (t, *J* = 3.2 Hz, 1H), 7.72 (s, 1H), 7.61-7.58 (m, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.50-7.45 (m, 4H), 7.18 (t, *J* = 8.8 Hz, 2H), 4.31 (t, *J* = 7.6 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 55.1, 115.4 (d, *J* = 21.2 Hz, 2C), 123.9, 125.2, 125.6, 125.8, 126.3, 128.3, 128.5 (2C), 128.8 (2C), 130.15, 130.18 (d, *J* = 25.2 Hz, 2C), 131.6, 133.9, 135.5, 135.9, 136.2 (d, *J* = 10.4 Hz), 139.6, 162.1 (d, *J* = 245.0 Hz), 170.8.

IR (cm^{-1}) 1650, 1504, 1446; HRMS (ES^+): calcd for $C_{25}H_{18}FNONa$ $(M+Na)^+$ 390.1270, found 390.1270.



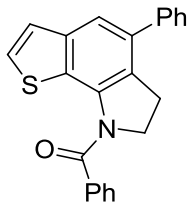
***N*-benzoyl-4-methoxyphenyl-2,3-dihydro-benzo[g]indole (4.22e)**.

The treatment of diene **4.12e** (0.055 g, 0.12 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0027 g, 0.012 mmol, 0.1 equiv) and NaOAc (0.011 g, 0.13 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded benzoindoline **4.22e** (0.03 g, 66%) as colorless oil: R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.84 (m, 3H), 7.80 (d, *J* = 5.6 Hz, 1H), 7.73 (s, 1H), 7.61-7.50 (m, 3H), 7.49-7.43 (m, 4H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.30 (t, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.23 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 55.1, 55.3, 113.9 (2C), 123.6, 125.2, 125.3, 125.6, 126.1, 128.2, 128.5 (2C), 128.8 (2C), 129.6 (2C), 130.4, 131.5, 132.6, 134.0, 136.0, 136.1, 139.4, 159.0, 170.7.

IR (cm^{-1}) 1650, 1446, 1074; HRMS (ES^+): calcd for $C_{26}H_{21}NO_2Na$ $(M+Na)^+$ 402.1470, found 402.1466.



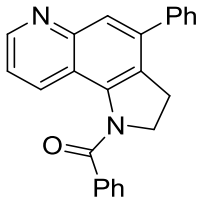
***N*-benzoyl-5-phenyl-7,8-dihydro-thieno[3,2-g]indole (4.24)**.

The treatment of diene **4.12f** (0.05 g, 0.11 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0025 g, 0.011 mmol, 0.1 equiv) and NaOAc (0.001 g, 0.012 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded pyrrolobenzothiophene **4.24** (0.018 g, 45%) as a colorless oil along with unreacted diene **4.12f** (0.020 g, 31%) as a colorless heavy oil: R_f = 0.45 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, *J* = 1.2 Hz, 1H), 7.79 (t, *J* = 2.0 Hz, 1H), 7.71 (s, 1H), 7.56-7.52 (m, 2H), 7.51-7.47 (m, 6H), 7.42-37 (m, 2H), 4.23 (t, *J* = 7.6 Hz, 2H), 3.25 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.0, 53.7, 120.9, 123.3, 127.2, 127.3, 127.7, 128.3, 128.4 (2C), 128.50 (2C), 128.51 (2C), 128.58 (2C), 131.3, 135.2, 135.7, 138.0, 140.3, 141.5, 168.5.

IR (cm^{-1}) 1637, 1490, 1398; HRMS (ES^+): calcd for $C_{23}H_{17}NOSNa$ $(M+Na)^+$ 378.0929, found 378.0934.



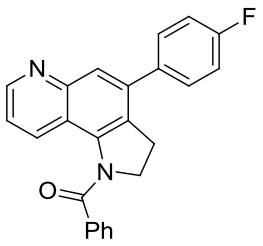
***N*-benzoyl-(4-phenyl-2,3-dihydro-pyrrolo[2,3-f]quinoline (4.25a)**.

The treatment of diene **4.12g** (0.032 g, 0.07 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0016 g, 0.007 mmol, 0.1 equiv) and NaOAc (0.0063 g, 0.077 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded pyrroloquinoline **4.25a** (0.02 g, 77%) as a colorless oil: R_f = 0.2 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.62-7.47 (m, 7H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.38 (dd, *J* = 8.4 Hz, *J* = 4.0 Hz, 1H), 4.33 (t, *J* = 7.6 Hz, 2H), 3.27 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.7, 55.2, 119.5, 120.0, 127.1, 127.9, 128.2, 128.5 (2C), 128.6 (2C), 128.70 (2C), 128.77 (2C), 130.9, 131.8, 134.4, 135.5, 139.3, 139.4, 140.1, 149.8, 170.9.

IR (cm^{-1}) 1649, 1556, 1490; HRMS (ES^+): calcd for $C_{24}H_{19}N_2O$ $(M+H)^+$ 351.1497, found 351.1490.



***N*-benzoyl-4-fluorophenyl-2,3-dihydro-pyrrolo[2,3-f]quinoline (4.25b)**.

The treatment of diene **4.12h** (0.03 g, 0.067 mmol, 1.0 equiv) with $Pd(OAc)_2$ (0.0015 g, 0.0067 mmol, 0.1 equiv) and NaOAc (0.006 g, 0.07 mmol, 1.1 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (2:3) afforded pyrroloquinoline **4.25b** (0.016 g, 65%) as a yellow oil: R_f = 0.3 (EtOAc/Hexane 3:7).

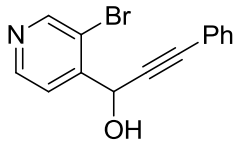
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.55-7.51 (m, 4H), 7.38 (dd, *J* = 8.4 Hz, *J* = 4.0 Hz, 1H), 7.19 (t, *J* = 8.8 Hz, 2H), 4.34 (t, *J* = 7.6 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 30.6, 55.1, 115.7 (d, *J* = 21.3 Hz, 2C), 119.4, 120.2, 127.3, 128.6 (2C), 128.7 (2C), 130.1 (d, *J* = 8.1 Hz, 2C), 130.6, 131.8, 134.0, 135.4, 130.5 (d, *J* = 3.2 Hz), 138.8, 139.4, 148.1, 150.3, 162.5 (d, *J* = 246 Hz), 171.0.

IR (cm^{-1}) 1637, 1440, 1400; HRMS (ES^+): calcd for $C_{24}H_{17}FN_2ONa$ $(M+Na)^+$ 391.1223, found 391.1231.

General procedure for synthesis of propargyl alcohols 4.36a-b:

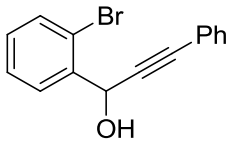
To a cooled solution of phenylacetylene (1.1 equiv) at -75^{o}C under argon, added *n*-BuLi (2.5 M in Hexane, 1.0 equiv) dropwise and stirred the resulting yellow solution for 1 h at -75^{o}C. Then quickly added the THF solution of aldehyde **4.32a-b** and stirred for 1 h. After this the solution was warmed to 0^{o}C and stirred for 1 h and then at rt for 4 h. Quenched the reaction mixture with saturated solution of NH_4Cl, extracted with (2 x 25 mL) ethylacetate. The combined organic layer was washed with brine, dried over anhydrous magnesium sulphate and evaporated to dry. The crude propargyl alcohols were used as such for subsequent reactions and were not fully characterized.



1-(3-bromopyridin-4-yl)-3-phenylprop-2-yn-1-ol (4.36a).

The treatment of aldehyde **4.32a** (0.07 g, 0.38 mmol, 1.0 equiv) with phenylacetylene (40 µL, 0.42 mmol, 1.1 equiv) and *n*-BuLi (144 µL, 0.38 mmol, 1.0 equiv) according to the general procedure described above, produced crude **4.36a** (0.095 g, 76%) as a light brown powder. The reaction was clean as analyzed by TLC and ^{1}H NMR. R_f = 0.25 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.61 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 5.2 Hz, 1H), 7.48-7.44 (m, 2H), 7.38-7.33 (m, 3H), 5.93 (s, 1H), 3.29 (br s, 1H).



1-(2-bromophenyl)-3-phenylprop-2-yn-1-ol (4.36b).

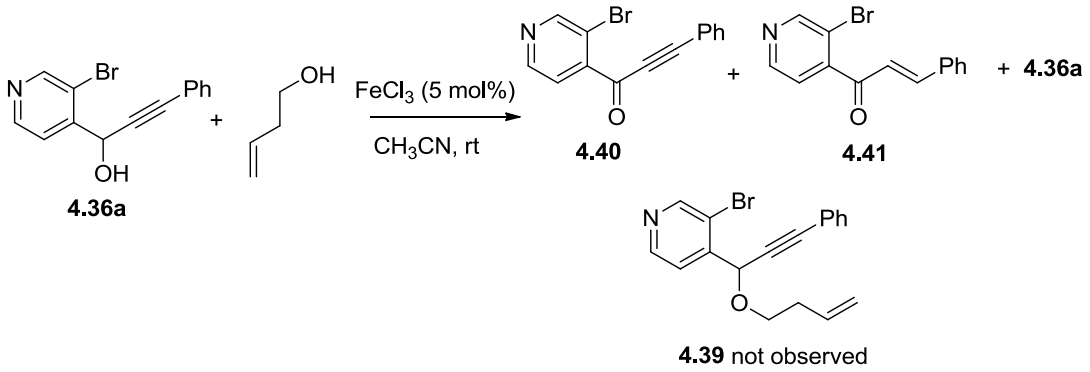
The treatment of aldehyde **4.32b** (0.192 g, 1.04 mmol, 1.0 equiv) with phenylacetylene (109 µL, 1.14 mmol, 1.1 equiv) and *n*-BuLi (394 µL, 1.04 mmol, 1.0 equiv) according to the general procedure described above, produced crude **4.36b** (0.251 g, 86%) as a clear oil. The reaction was clean as analyzed by TLC and ^{1}H NMR. R_f = 0.35 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.62 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.41 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.36-7.32 (m, 3H), 7.24 (td, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 6.04 (s, 1H), 2.38 (br , 1H).

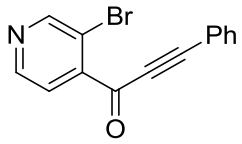
General procedure for Fe-catalyzed substitution of propargyl alcohol (4.36a-b):

To the solution of propargyl alcohol **4.36a-b** (1.0 equiv) in acetonitrile under argon, added neat 3-Buten-1-ol (3.0 equiv) and $FeCl_3$ (0.05 equiv) successively and stirred the resulting brown solution at 60^{o}C for 18 h. Cooled the reaction mixture and evaporated the volatile components. The crude residue was adsorbed on silica and purified by flash column chromatography.

1-(3-bromopyridin-4-yl)-3-phenylprop-2-yn-1-one (4.40) and **1-(3-bromopyridin-4-yl)-3-phenylprop-2-en-1-one (4.41)**.



The treatment of crude propargyl alcohol **4.36a** (0.11 g, 0.38 mmol, 1.0 equiv) with 3-Buten-1-ol (99 µL, 1.15 mmol, 3.0 equiv), and $FeCl_3$ (0.0032 g, 0.02 mmol, 0.05 equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (3:7) afforded ynone **4.40** (0.023 g, 21%) as a colorless oil and further elution EtOAc/Hexane (2:3) afforded enone **4.41** (0.019g, 17%) as a colorless oil along with unreacted **4.36a**



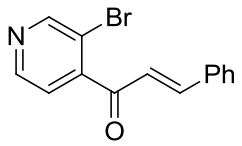
Analytical data for Ynone 4.40:

R_f = 0.35 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.73 (d, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 4.8 Hz, 1H), 7.70-7.66 (m, 1H), 7.57-7.51 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 2H),

^{13}C NMR (125 MHz, $CDCl_3$) δ 87.4, 96.6, 117.8, 119.2, 124.5, 128.8 (2C), 131.6, 133.6 (2C), 143.9, 148.7, 153.9, 176.1;

IR (cm^{-1}) 2194, 1658, 1488; HRMS (ES^+) calcd for $C_{14}H_9BrNO$ $(M+H)^+$, 285.9868, found 285.9861.



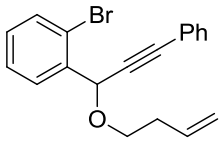
Analytical data for enone 4.41:

R_f = 0.30 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.68 (d, *J* = 4.8 Hz, 1H), 7.61-7.54 (m, 2H), 7.48-7.38 (m, 4H), 7.33 (d, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 16.4 Hz, 1H),

^{13}C NMR (125 MHz, $CDCl_3$) δ 117.4, 122.9, 124.8, 128.8 (2C), 129.1 (2C), 131.6, 133.7, 147.7, 148.60, 148.61, 152.0, 192.3,

IR (cm^{-1}) 1651, 1595, 1396; HRMS (ES^+): calcd for $C_{14}H_{11}BrNO$ $(M+H)^+$ 288.0024, found 288.0017.



1-bromo-2-(1-(but-3-en-1-yloxy)-3-phenylprop-2-yn-1-yl) benzene (4.38).

The treatment of crude propargyl alcohol **4.36b** (0.045 g, 0.16 mmol, 1.0 equiv) with 3-Buten-1-ol (24 µL, 0.48 mmol, 3.0 equiv), and $FeCl_3$ (0.0013 g, 0.008 mmol, 0.05

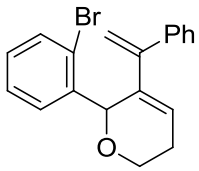
equiv) according to the general procedure described above, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:9) afforded enyne **4.38** (0.031 g, 75%) as a colorless oil along with unreacted propargyl alcohol **4.36b** (0.012 g, 22%)

R_f = 0.8 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.60 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.53-7.49 (m, 2H), 7.39 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.36-7.31 (m, 3H), 7.22 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 5.96-5.85 (m, 1H), 5.70 (s, 1H), 5.16 (dq, *J* = 12.4 Hz, *J* = 1.6 Hz, 1H), 5.08 (dq, *J* = 10.0 Hz, *J* = 1.2 Hz, 1H), 3.91 (dt, *J* = 9.2 Hz, *J* = 6.8 Hz, 1H), 3.68 (dt, *J* = 8.8 Hz, *J* = 7.2 Hz, 1H), 2.48 (q, *J* = 6.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1, 68.6, 71.3, 86.4, 87.3, 116.4, 122.5, 123.5, 127.7, 128.3 (2C), 128.5, 129.3, 129.9, 131.8 (2C), 132.9, 135.0, 138.0.

IR (cm^{-1}) 1409, 1150; HRMS (ES^+): calcd for $C_{19}H_{17}BrONa$ $(M+Na)^+$ 363.0360, found 363.0364.



6-(2-bromophenyl)-5-(1-phenylvinyl)-3,6-dihydro-2H-pyran (4.43).

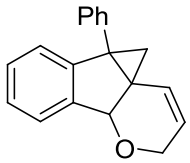
The treatment of enyne **4.42** (0.025 g, 0.07 mmol, 1.0 equiv) with Grubbs II catalyst (0.006 g, 0.007 mmol, 0.1 equiv) according to the general procedure described above

for **4.13a-e** and **4.13g-i**, followed by flash chromatography over silica eluting with EtOAc/Hexane (1:4) afforded pyran diene **4.43** (0.02 g, 79%) as a colorless oil: R_f = 0.55 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.41 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.35-7.30 (m, 4H), 7.18 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.13-6.08 (m, 1H), 5.95 (s, 1H), 4.92 (d, *J* = 17.0 Hz, 2H), 3.76 (dd, *J* = 4.8 Hz, *J* = 2.0 Hz, 2H), 2.49-2.38 (m, 1H), 2.36-2.33 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 59.5, 74.7, 114.2, 125.6, 126.9, 127.4, 128.0 (2C), 128.51, 128.54 (2C), 129.5, 130.3, 133.3, 137.7, 138.5, 140.9, 147.5.

IR (cm^{-1}) 1396, 1190; HRMS (ES^+): calcd for $C_{19}H_{17}BrONa$ $(M+Na)^+$ 363.0360, found 363.0366.



5a-phenyl-2,5,5a,9b-tetrahydrocyclopropa[2,3]indeno[1,2-b]pyran (4.44).

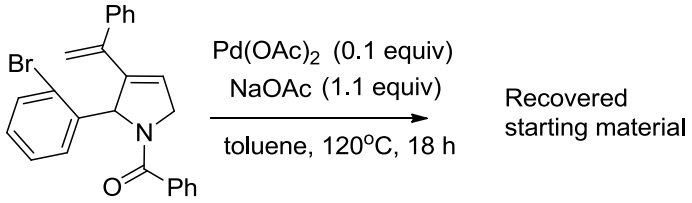
The diene **4.43** (0.02 g, 0.06 mmol, 1.0 equiv) was treated with $Pd(OAc)_2$ (0.0013 g, 0.006 mmol, 0.1 equiv), Cs_2CO_3 (0.039 g, 0.12 mmol, 2.0 equiv) and PPh_3 (0.003 g, 0.012 mmol, 0.2 equiv) according to the general procedure described for **4.21a-e** and **4.23a-c**. Repeated purification via silica column chromatography did not afford pure **4.44**.

R_f = 0.5 (EtOAc/Hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.43 (m, 2H), 7.41-7.36 (m, 3H), 7.33-7.30 (m, 1H), 7.25-7.22 (m, 2H), 7.02-6.97 (m, 1H), 5.93 (ddd, *J* = 9.6 Hz, *J* = 4.4 Hz, *J* = 1.6 Hz, 1H), 5.27 (ddd, *J* = 10.4 Hz, *J* = 3.6 Hz, *J* = 1.2 Hz, 1H), 4.93 (s, 1H), 4.50-4.44 (m, 1H), 4.36-4.28 (m, 1H), 1.87 (d, *J* = 5.2 Hz, 1H), 1.12 (d, *J* = 4.8 Hz, 1H),

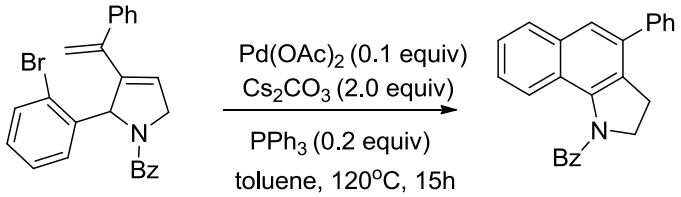
HRMS (ES^+): calcd for $C_{19}H_{16}ONa$ $(M+Na)^+$ 283.1099, found 283.1090.

Development of a one-pot protocol for the synthesis of benzoindolines 4.22a, 4.22 c, 4.22e and **pyrroloquinoline 4.22g**:



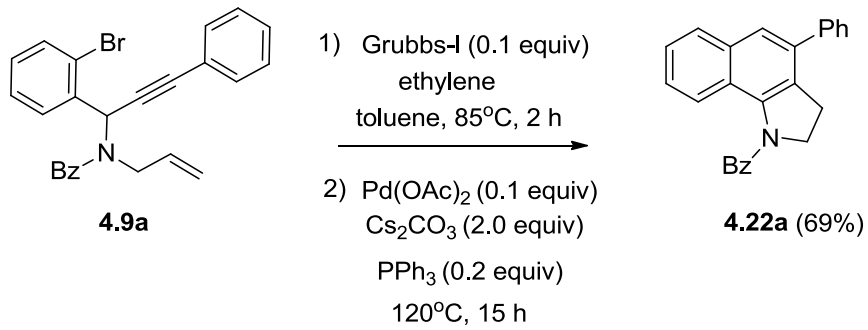
4.12a

The diene **4.12a** (0.067 g, 0.15 mmol, 1.0 equiv) was treated with $Pd(OAc)_2$ (0.0038 g, 0.015 mmol, 0.1 equiv), NaOAc (0.014 g, 0.17 mmol, 1.1 equiv) according to the general procedure described for **4.22a-e** and **4.25a-c**. Toluene was used instead of DMF and no workup was done. Instead, reaction was loaded on a silica column and was purified by flash chromatography over silica eluting with EtOAc/Hexane (1:9) to recover the diene **4.12a** (0.060 g, 89%).

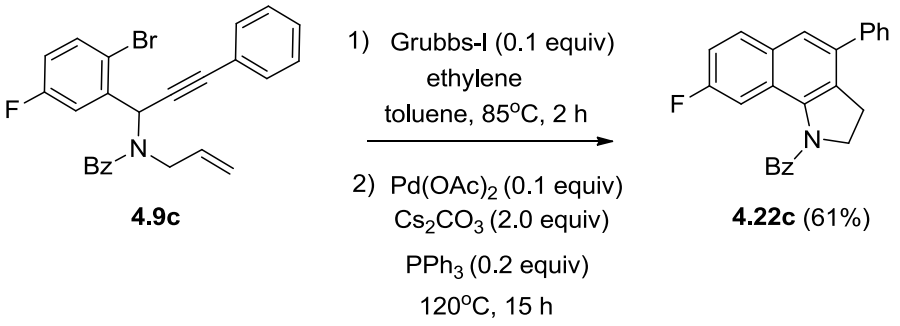


4.12a **4.22a** (65%)

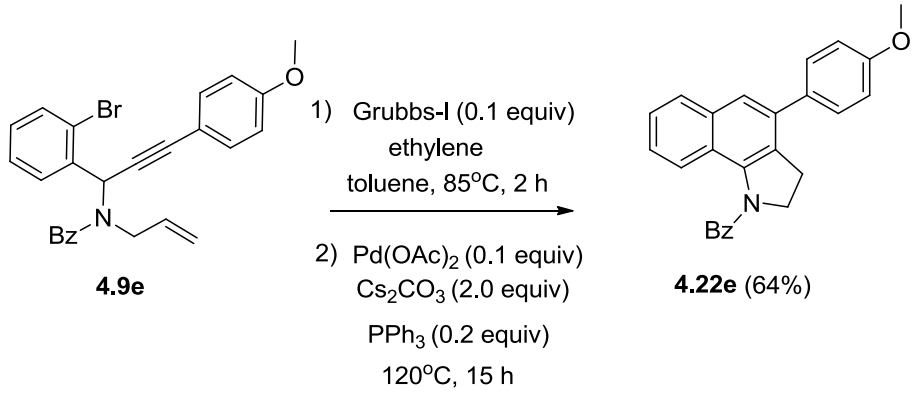
The diene **4.12a** (0.051 g, 0.12 mmol, 1.0 equiv) was treated with $Pd(OAc)_2$ (0.0027 g, 0.012 mmol, 0.1 equiv), Cs_2CO_3 (0.078 g, 0.24 mmol, 2.0 equiv) and PPh_3 (0.0063 g, 0.024 mmol, 0.2 equiv) according to the general procedure described for **4.21a-e** and **4.23a-c**. Toluene was used instead of DMF and no workup was done. Instead, reaction was loaded on a silica column and was purified by flash chromatography over silica eluting with EtOAc/Hexane (1:9) to afford benzoindoline **4.22a** (0.027 g, 65%) as a white solid.



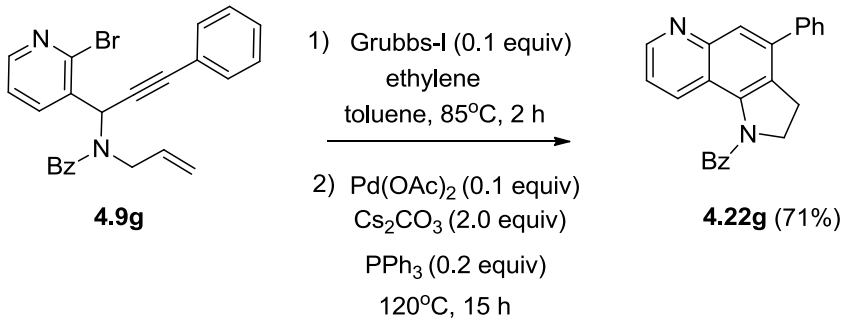
(Ethylene was bubbled through, 5 min) the solution of **4.9a** (0.08 g, 0.18 mmol) in toluene (4 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs I catalyst (0.015 g, 0.018 mmol) was added as a solid and the reaction mixture was stirred at 85°C under ethylene atmosphere for 2 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.0042 g, 0.018 mmol), PPh_3 (0.012 g, 0.03 mmol), Cs_2CO_3 (0.097 g, 0.37 mmol) were added as solids. The reaction mixture was stirred at 120°C for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on a silica column and was eluted with EtOAc/Hexane (1:9) to afford pure benzoindoline **4.22a** (0.045 g, 69% yield) as a white solid.



(Ethylene was bubbled through, 5 min) the solution of **4.9c** (0.037 g, 0.08 mmol) in toluene (4 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs I catalyst (0.007 g, 0.008 mmol) was added as a solid and the reaction mixture was stirred at 85°C under ethylene atmosphere for 2 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.002 g, 0.008 mmol), PPh_3 (0.005 g, 0.017 mmol), Cs_2CO_3 (0.055 g, 0.17 mmol) were added as solids. The reaction mixture was stirred at 120°C for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on a silica column and was eluted with EtOAc/Hexane (1:9) to afford pure benzoindoline **4.22c** (0.019 g, 61% yield) as a heavy oil.



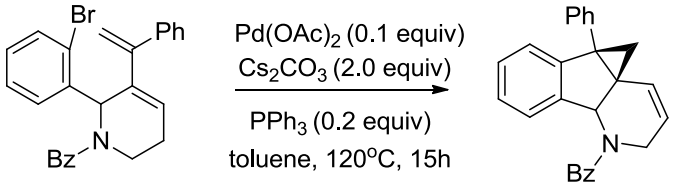
(Ethylene was bubbled through, 5 min) the solution of **4.9e** (0.04 g, 0.087 mmol) in toluene (4 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs I catalyst (0.008 g, 0.009 mmol) was added as a solid and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 2 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.002 g, 0.009 mmol), PPh_3 (0.005 g, 0.017 mmol), Cs_2CO_3 (0.055 g, 0.17 mmol) were added as solids. The reaction mixture was stirred at 120^{o}C for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on a silica column and was eluted with EtOAc/Hexane (1:4) to afford pure benzoindoline **4.22e** (0.021 g, 64% yield) as a colorless oil.



(Ethylene was bubbled through, 5 min) the solution of **4.9g** (0.051 g, 0.12 mmol) in toluene (4 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs I catalyst (0.01 g, 0.012 mmol) was added as a solid and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 2 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.003 g, 0.012 mmol), PPh_3 (0.009 g,

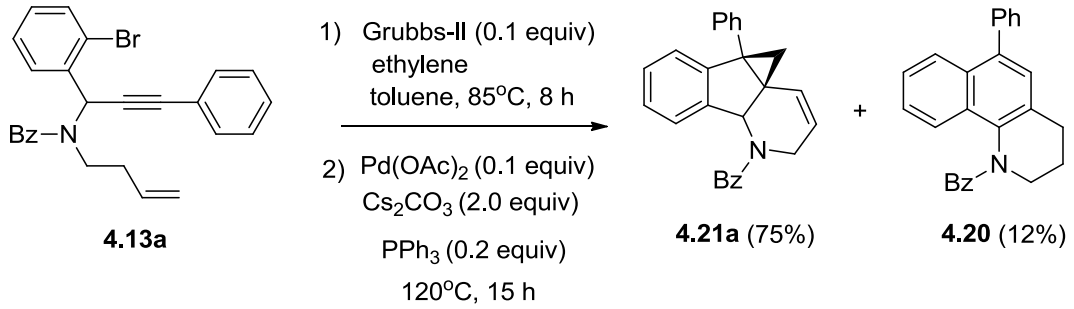
0.024 mmol), Cs_2CO_3 (0.078 g, 0.24 mmol) were added as solids. The reaction mixture was stirred at 120^oC for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on a silica column and was eluted with EtOAc/Hexane (2:3) to afford pure benzoindoline **4.22g** (0.03 g, 71% yield) as a colorless oil.

Development of a one-pot protocol for the synthesis of indenopyridines 4.21a, 4.21c, 4.21e and **phenanthrolines 4.23a-b**:

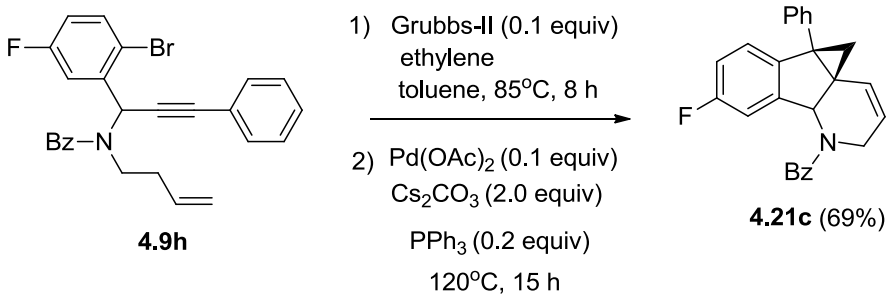


4.13a **4.21a** (77%)

The diene **4.13a** (0.049 g, 0.11 mmol, 1.0 equiv) was treated with $Pd(OAc)_2$ (0.0025 g, 0.011 mmol, 0.1 equiv), Cs_2CO_3 (0.072 g, 0.22 mmol, 2.0 equiv) and PPh_3 (0.008 g, 0.022 mmol, 0.2 equiv) according to the general procedure described for **4.21a-e** and **4.23a-c**. Toluene was used instead of DMF and no workup was done. Instead, the mixture was directly loaded on silica column and was purified by flash chromatography over silica eluting with EtOAc/Hexane (1:8) to afforded indenopyridine **4.21a** (0.031 g, 77%) as a white fluffy solid.

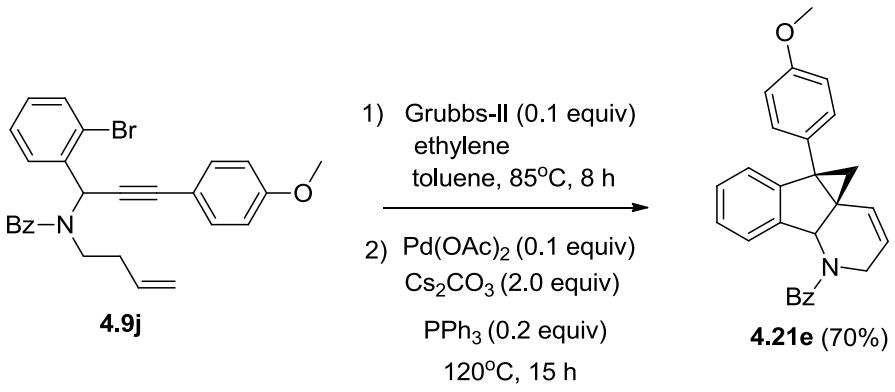


(Ethylene was bubbled through, 5 min) the solution of **4.9f** (0.103 g, 0.20 mmol) in toluene (10 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs II catalyst (0.02 g, 0.02 mmol) was added as solid, and the reaction mixture was stirred at 85°C under ethylene atmosphere for 8 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.0052 g, 0.02 mmol), PPh_3 (0.015 g, 0.04 mmol), Cs_2CO_3 (0.122 g, 0.46 mmol) were added as solids. The reaction mixture was stirred at 120°C for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on to silica column and was eluted with EtOAc/Hexane (1:8) to afford indenopyridine **4.21a** (0.063 g, 75%) as a white fluffy solid and benzoquinoline **4.20** (0.001 g, 12%) as a white solid.



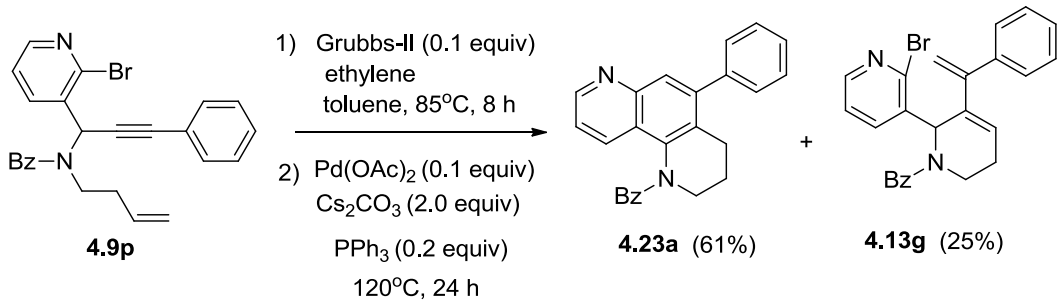
(Ethylene was bubbled through, 5 min) the solution of **4.9h** (0.041 g, 0.09 mmol) in toluene (4 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs II catalyst

(0.008 g, 0.009 mmol) was added as solid, and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 8 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.002 g, 0.009 mmol), PPh_3 (0.007 g, 0.018 mmol), Cs_2CO_3 (0.059 g, 0.18 mmol) were added as solids. The reaction mixture was stirred at 120^{o}C for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on to silica column and was eluted with EtOAc/Hexane (1:4) to afford indenopyridine **4.21c** (0.023 g, 69%) as a colorless heavy oil.

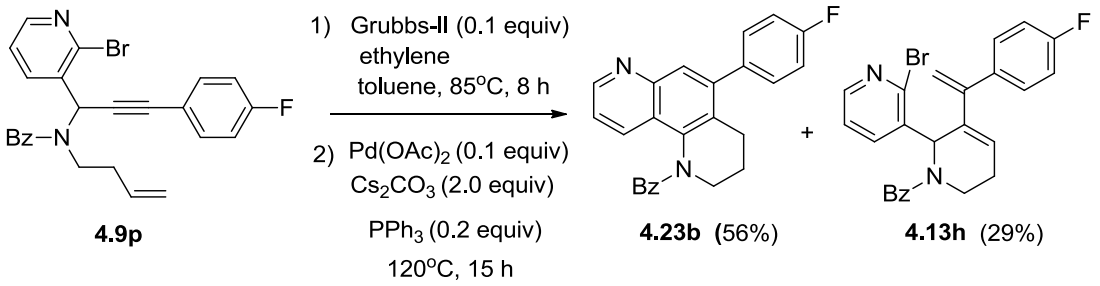


(Ethylene was bubbled through, 5 min) the solution of **4.9j** (0.032 g, 0.07 mmol) in toluene (3 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs II catalyst (0.006 g, 0.007 mmol) was added as solid, and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 8 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.002 g, 0.007 mmol), PPh_3 (0.005 g, 0.014 mmol), Cs_2CO_3 (0.046 g, 0.14 mmol) were added as solids. The reaction mixture was stirred at 120^{o}C for 15 h and cooled to rt. Upon evaporation of toluene

the crude mixture was loaded on to silica column and was eluted with EtOAc/Hexane (1:8) to afford indenopyridine **4.21e** (0.019 g, 70%) as a colorless oil.



(Ethylene was bubbled through, 5 min) the solution of **4.9p** (0.043 g, 0.1 mmol) in toluene (3 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs II catalyst (0.008 g, 0.01 mmol) was added as solid, and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 8 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.002 g, 0.01 mmol), PPh_3 (0.007 g, 0.02 mmol), Cs_2CO_3 (0.065 g, 0.2 mmol) were added as solids. The reaction mixture was stirred at 120^{o}C for 24 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on to silica column and was eluted with EtOAc/Hexane (2:3) to afford phenanthroline **4.23a** (0.022 g, 61%) as a light yellow powder and (0.011g, 25%) of RCM product **4.13g** was recovered.



(Ethylene was bubbled through, 5 min) the solution of **4.9q** (0.034 g, 0.07 mmol) in toluene (3 mL) in a 25 mL 2 neck RB fit with a reflux condenser. Grubbs II catalyst (0.006 g, 0.007 mmol) was added as solid, and the reaction mixture was stirred at 85^{o}C under ethylene atmosphere for 8 h. The reaction mixture was cooled to rt and purged with argon for 10 minutes. $Pd(OAc)_2$ (0.002 g, 0.007 mmol), PPh_3 (0.005 g, 0.014 mmol), Cs_2CO_3 (0.046 g, 0.14 mmol) were added as solids. The reaction mixture was stirred at 120^{o}C for 15 h and cooled to rt. Upon evaporation of toluene the crude mixture was loaded on to silica column and was eluted with EtOAc/Hexane (2:3) to afford phenanthroline **4.23b** (0.015 g, 56%) as a colorless oil and (0.01g, 29%) of RCM product **4.13h** was recovered.

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Appendix

Selected NMR Spectra, GC-MS Spectra and X-Ray Crystallographic Data

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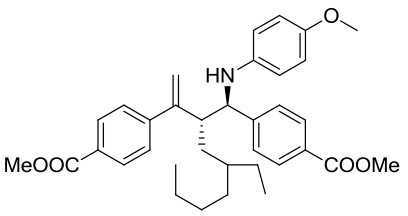
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HN
MeOOC
COOMe

3.8 (500 MHz)

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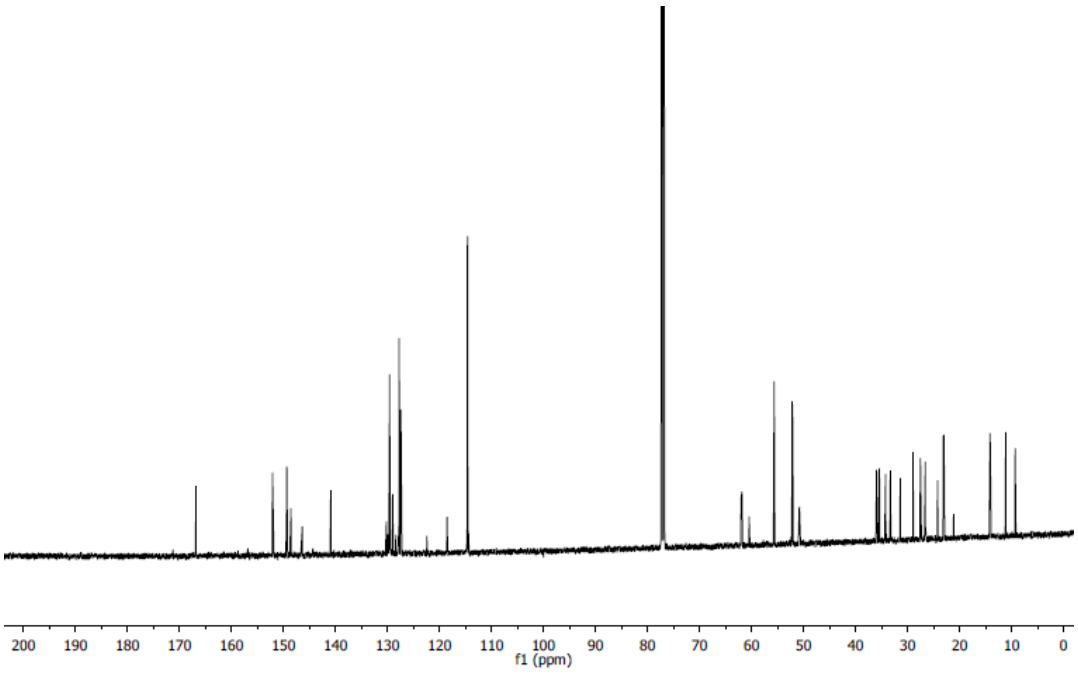
f1 (ppm)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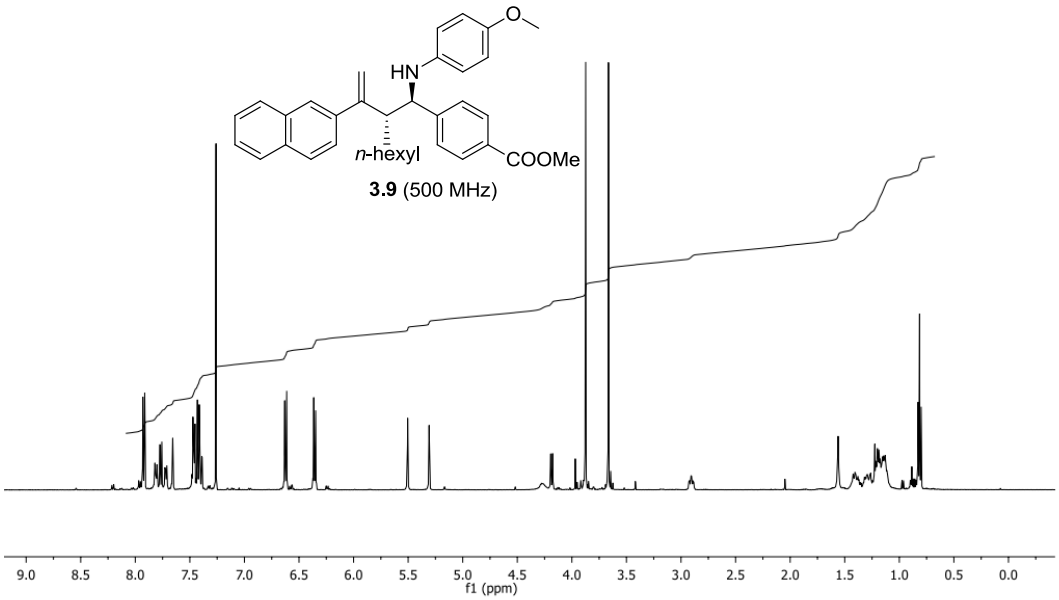
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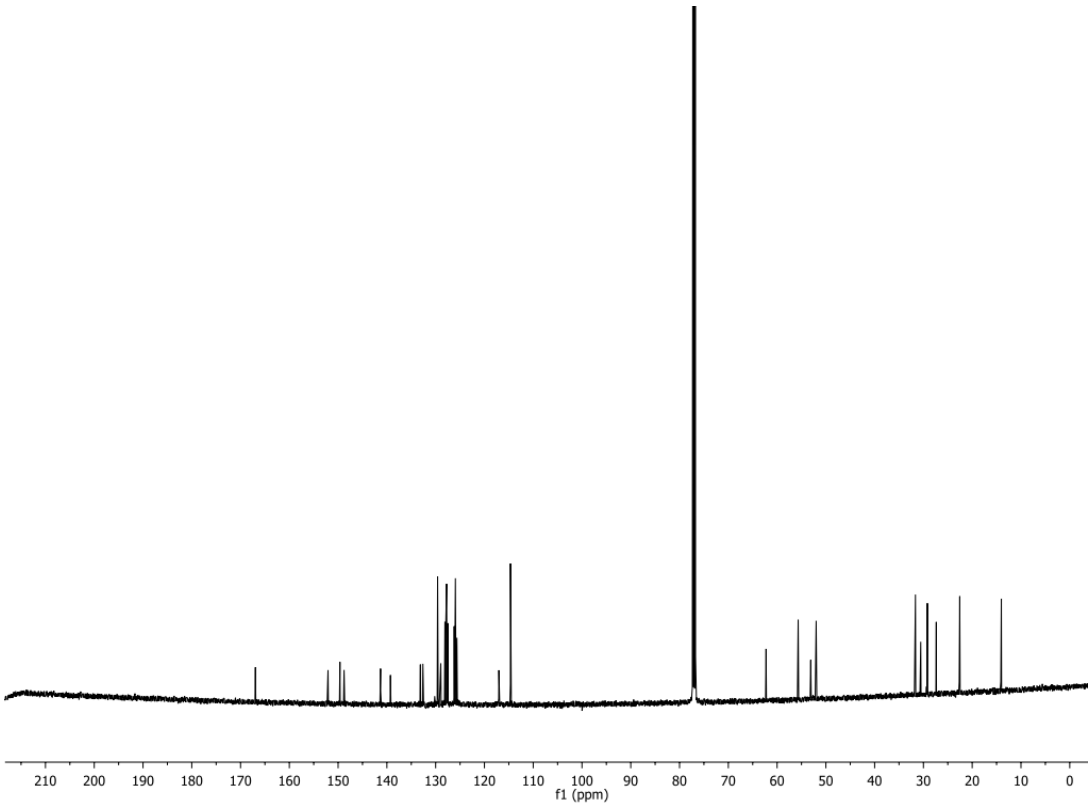
f1 (ppm)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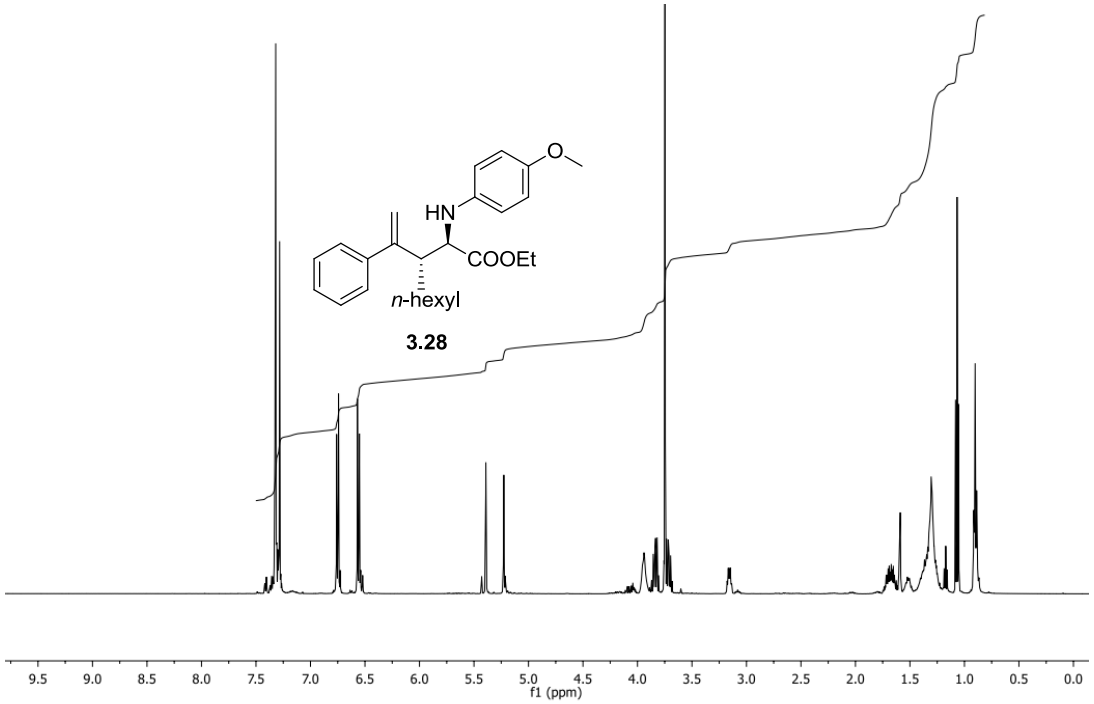
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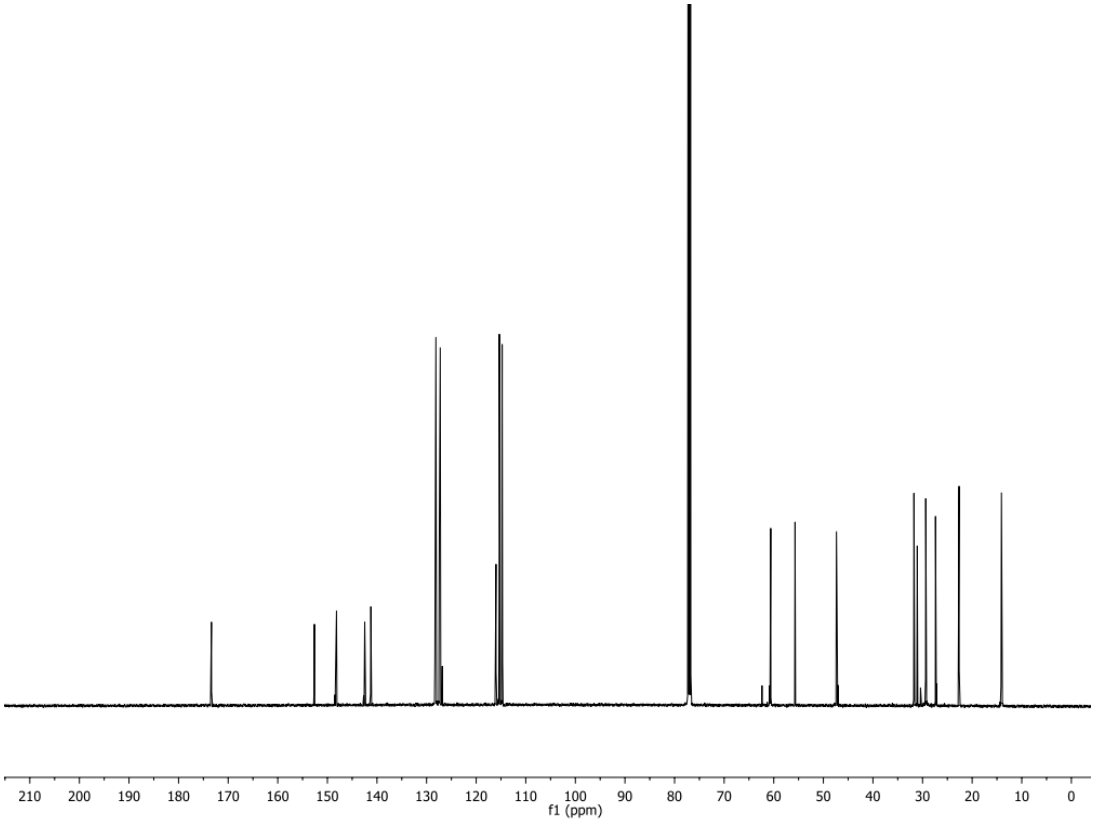
f1 (ppm)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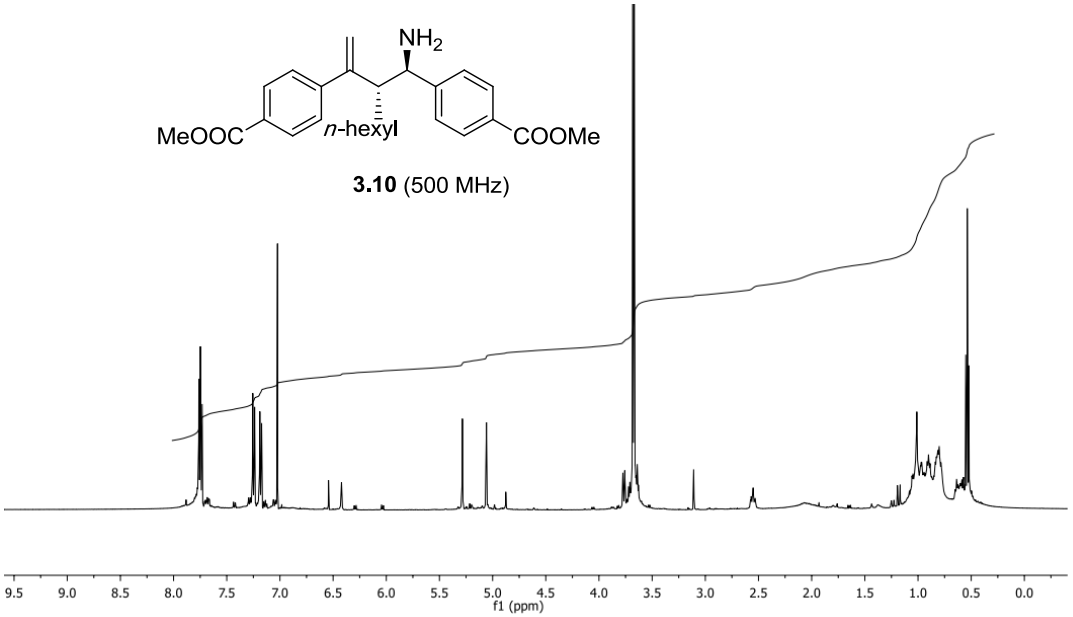
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n-hexyl
COOMe
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f1 (ppm)

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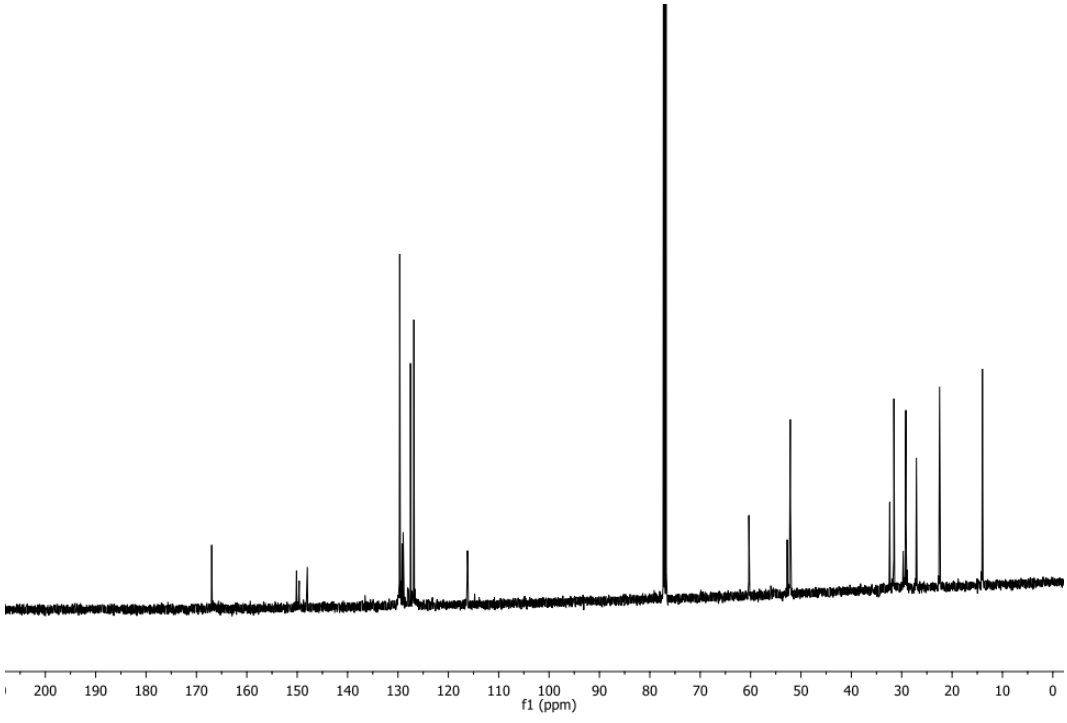
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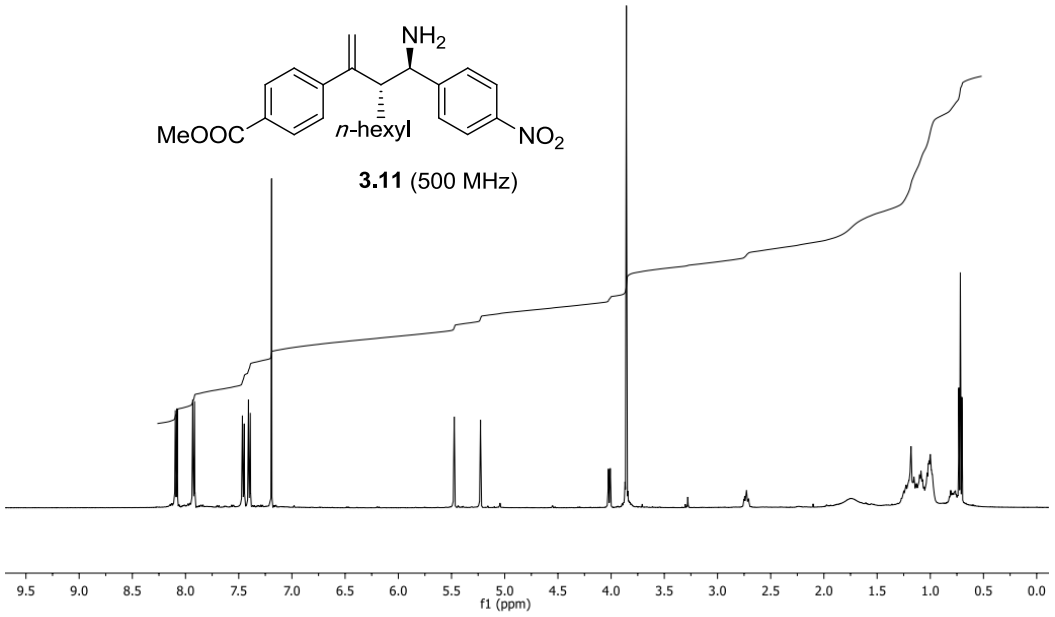
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n-hexyl
NO2
3.11 (500 MHz)
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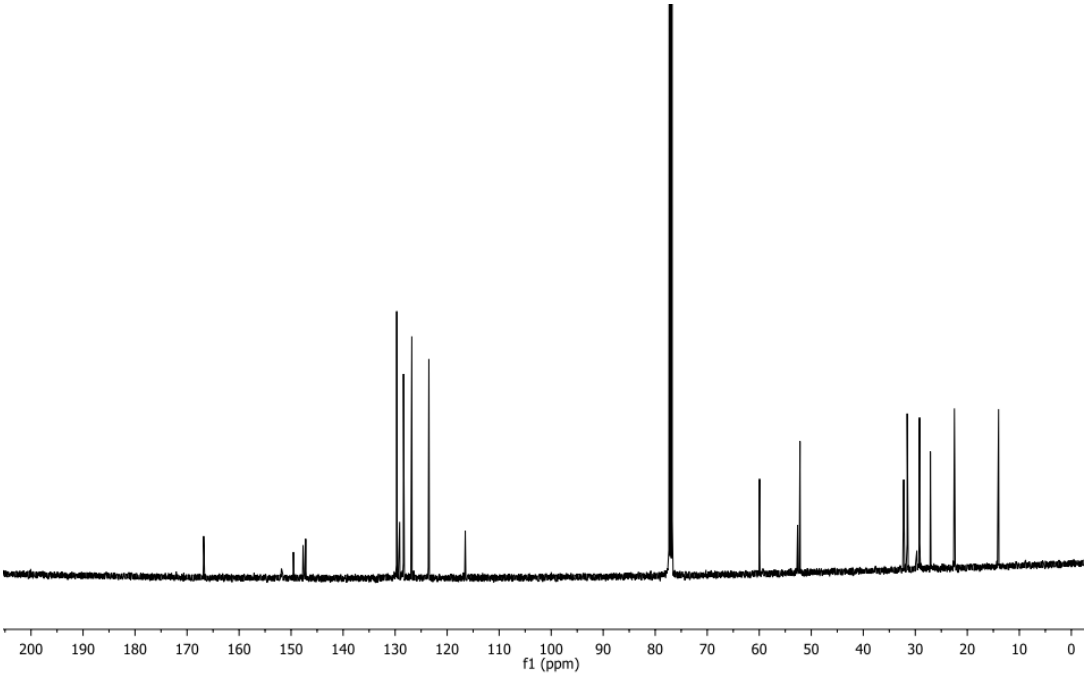
f1 (ppm)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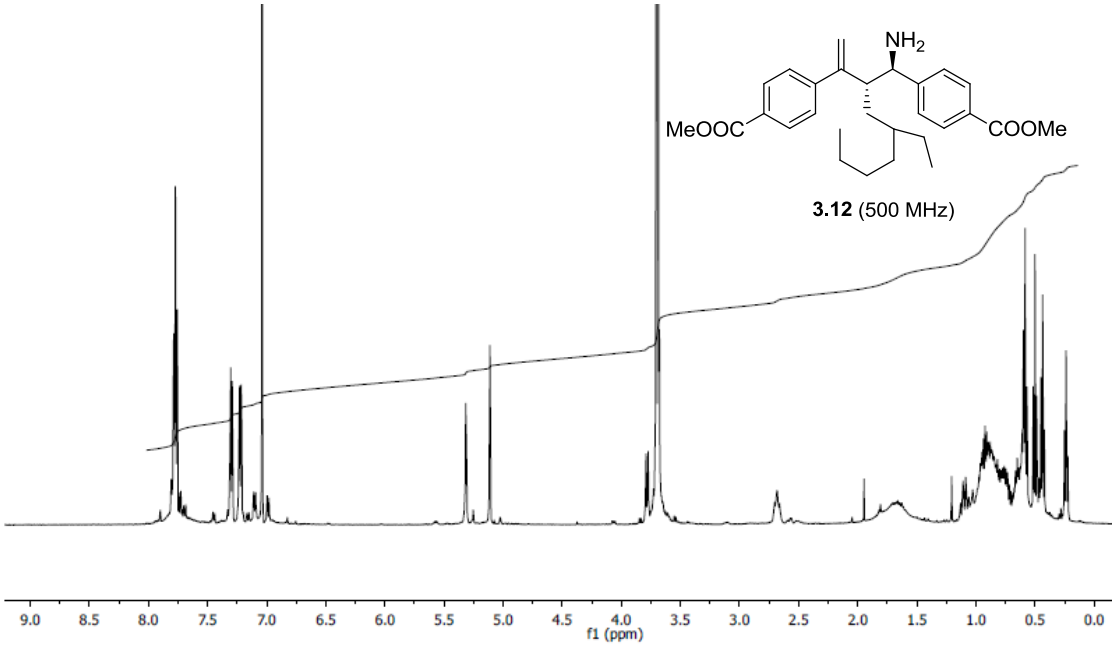
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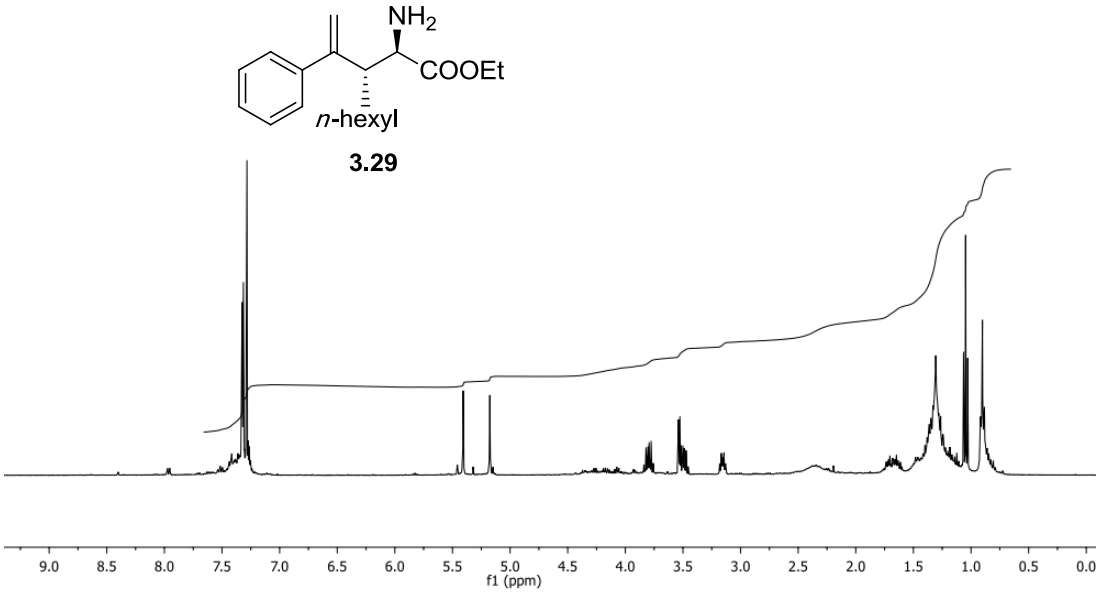
f1 (ppm)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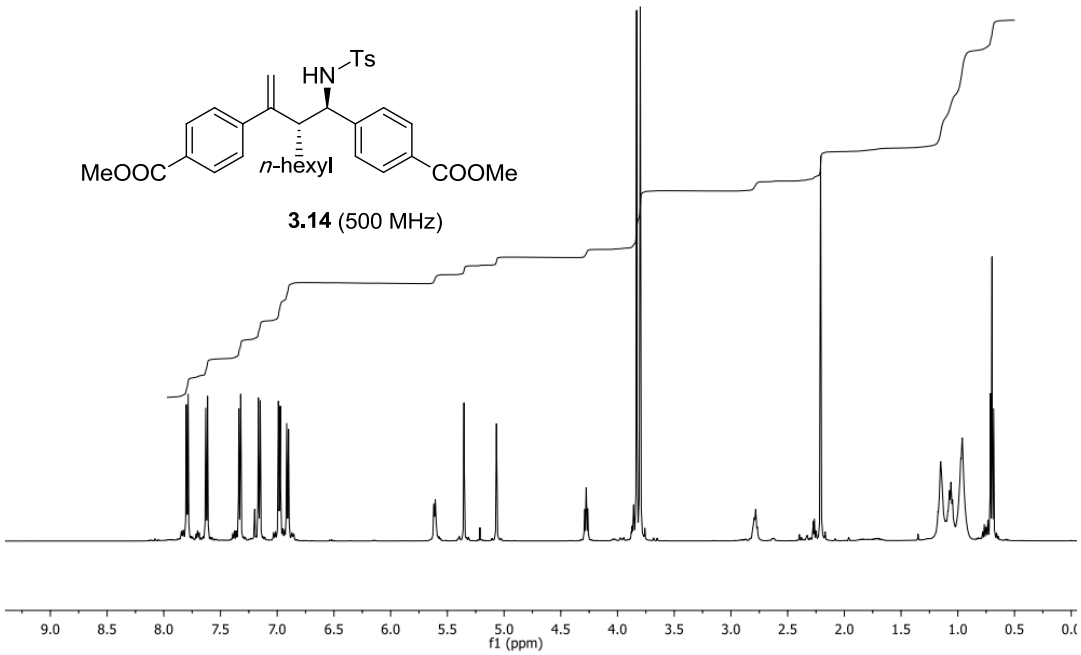
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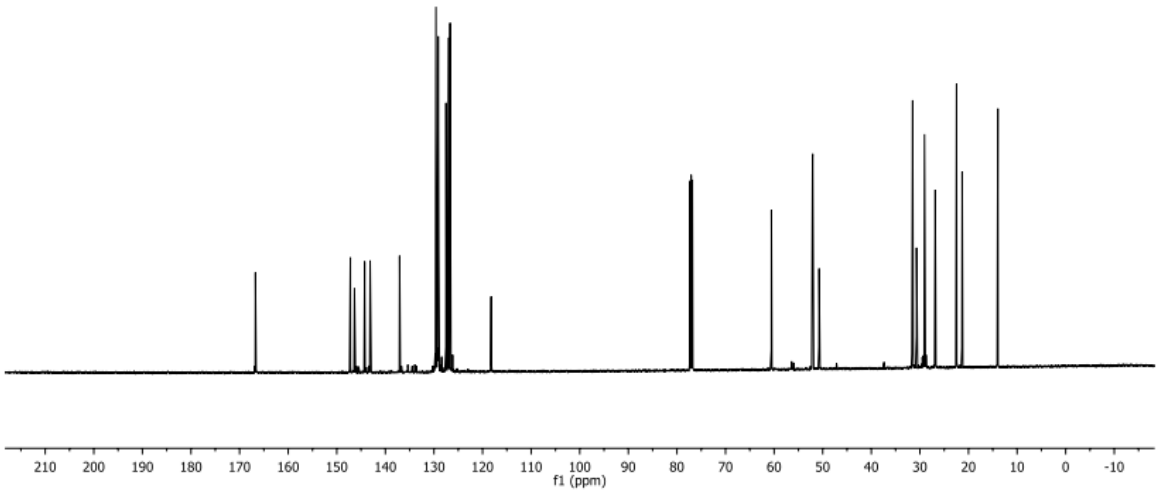
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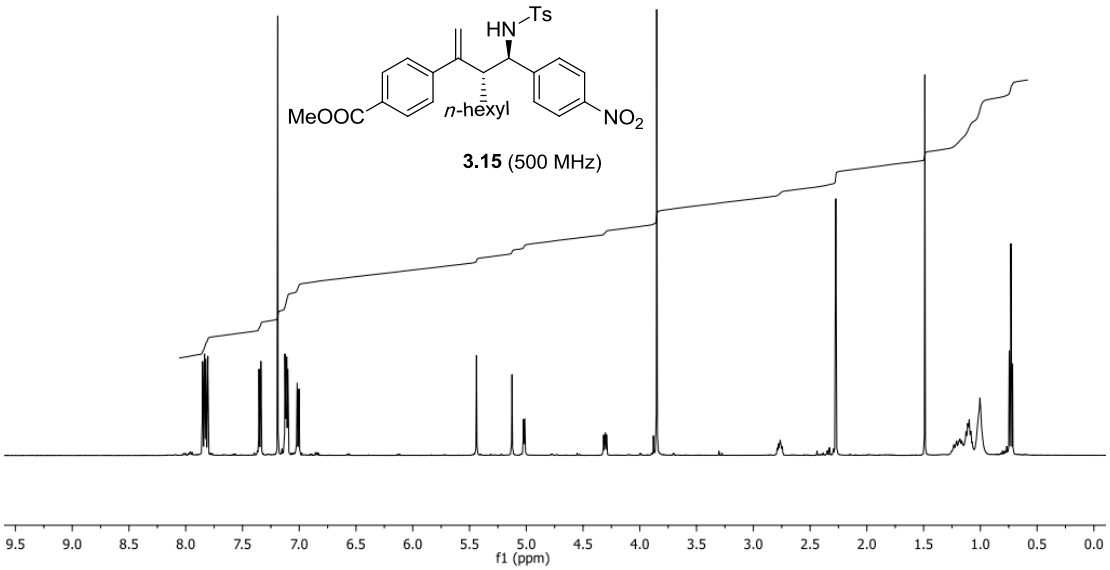
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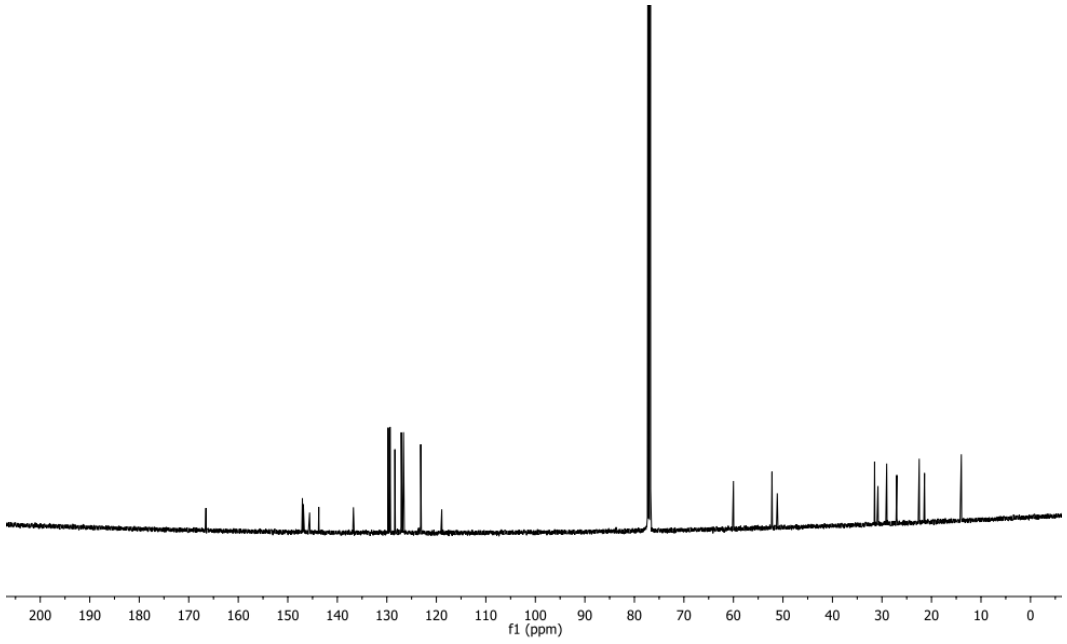
f1 (ppm)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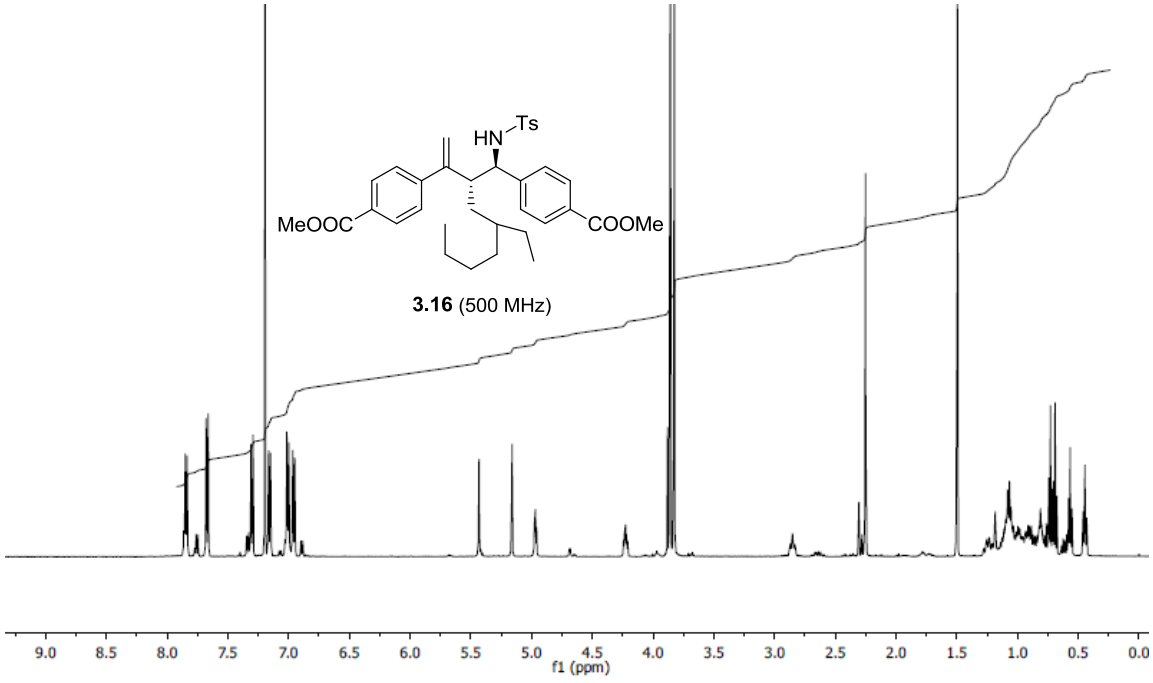
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Ts
MeOOC
COOMe
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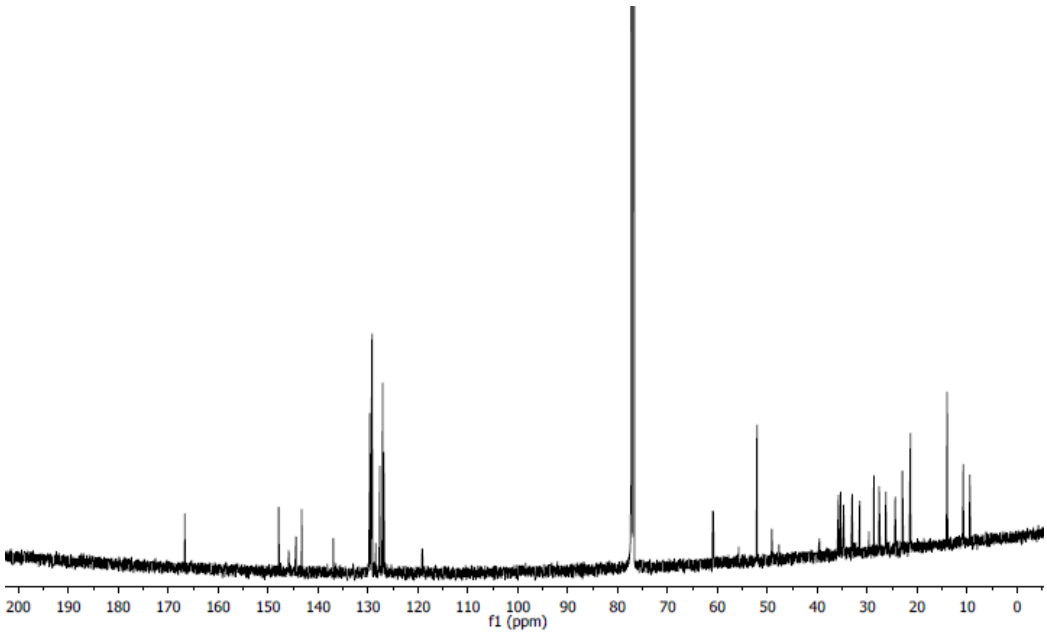
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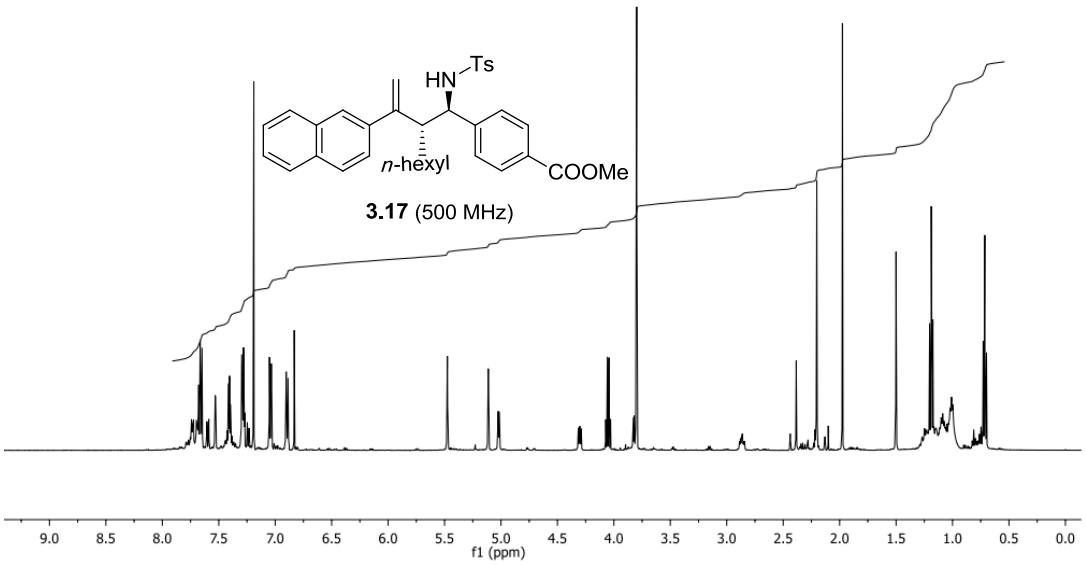
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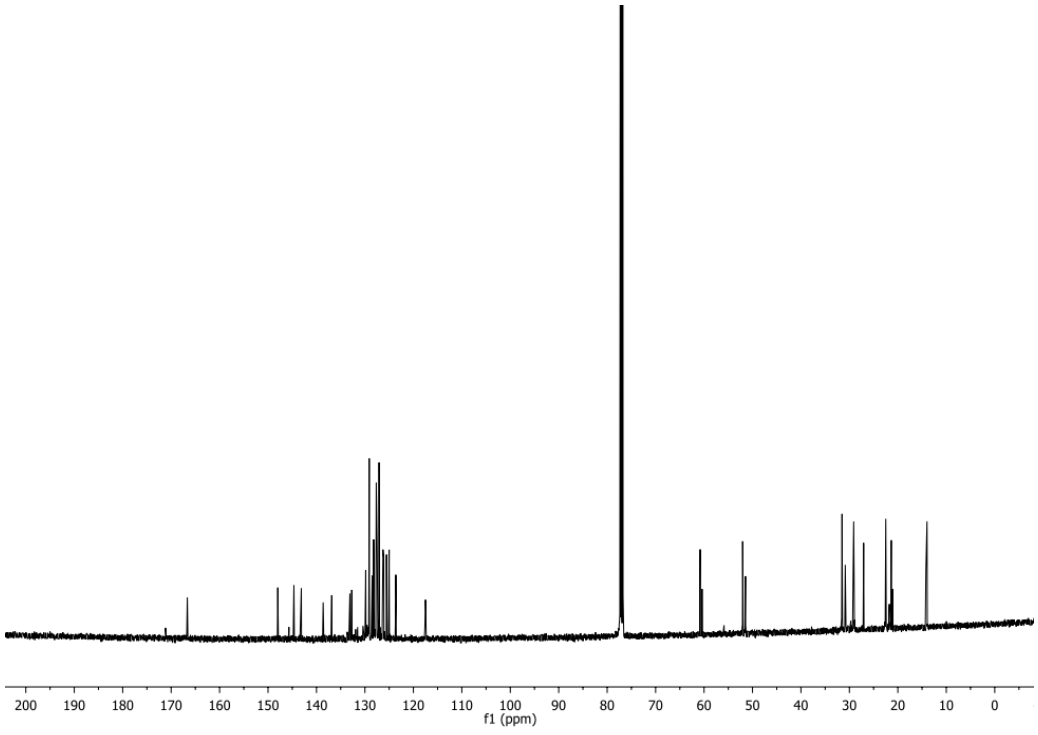
f1 (ppm)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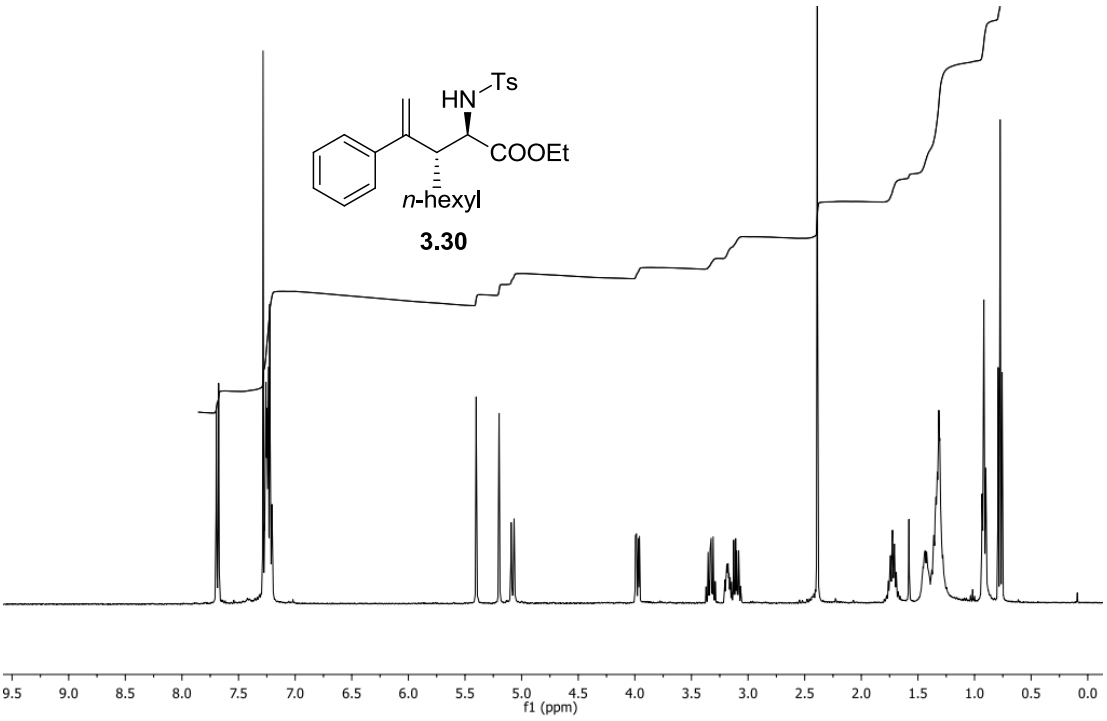
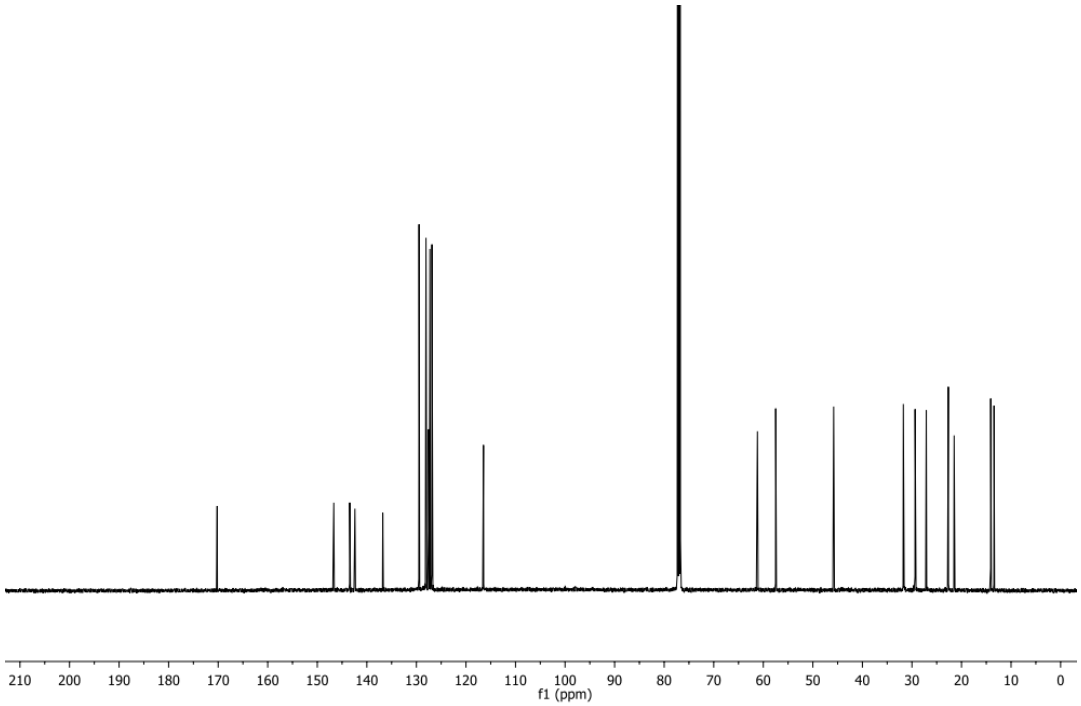
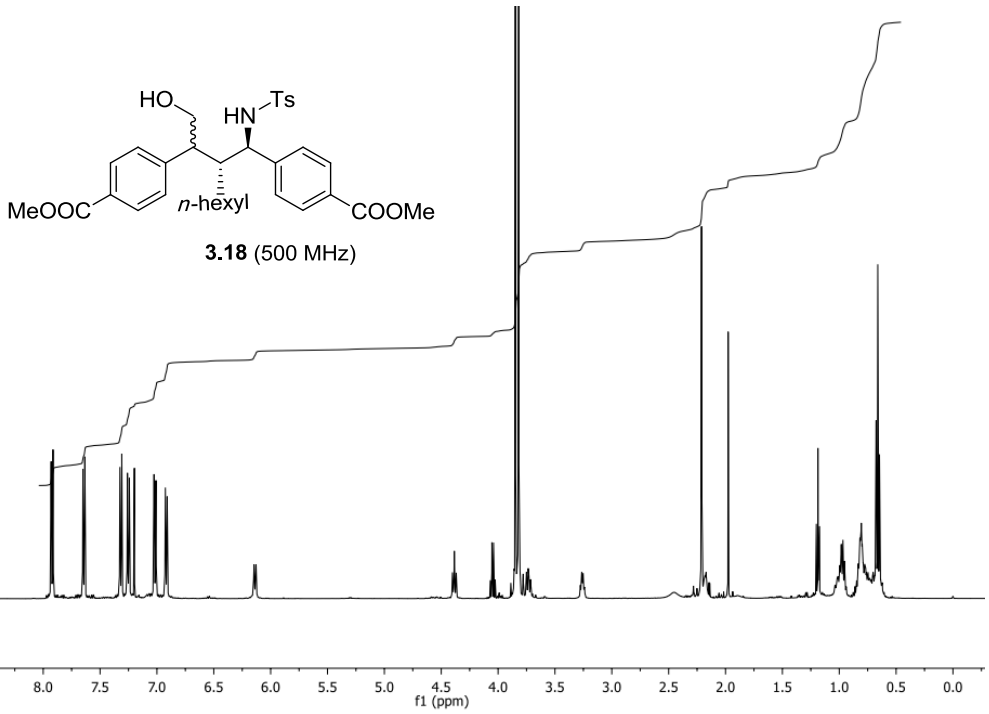
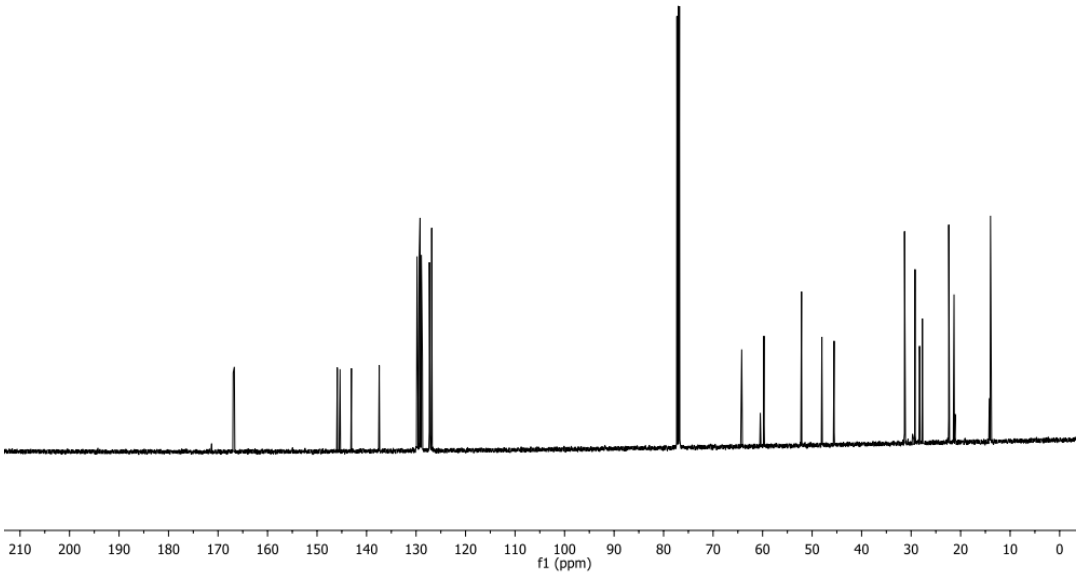
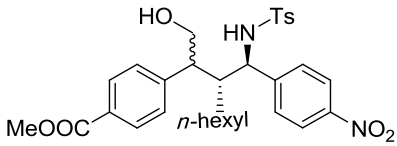
f1 (ppm)


HN
Ts
COOEt
n-hexyl
3.30
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

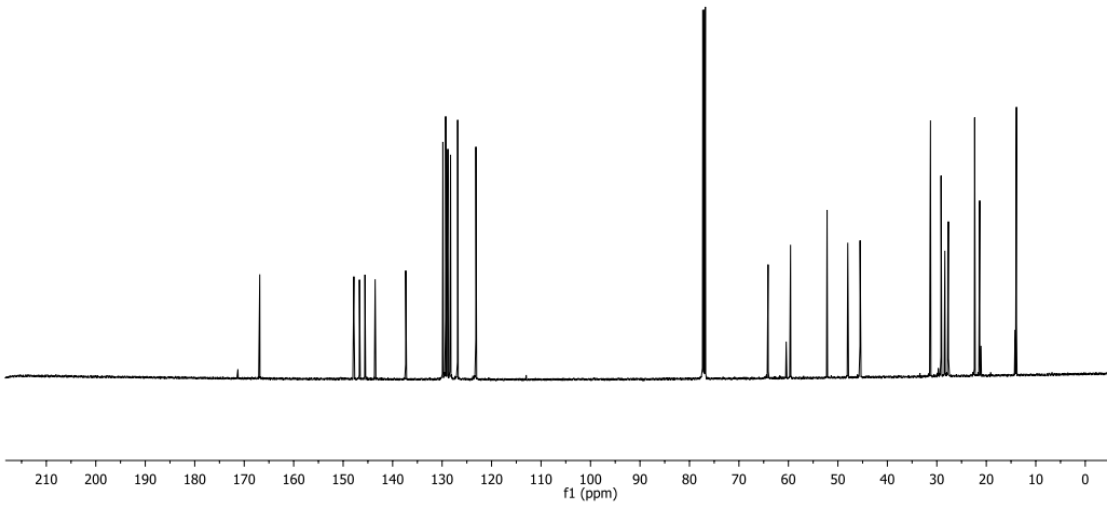

HO
HN
Ts
MeOOC
n-hexyl
COOMe
3.18 (500 MHz)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

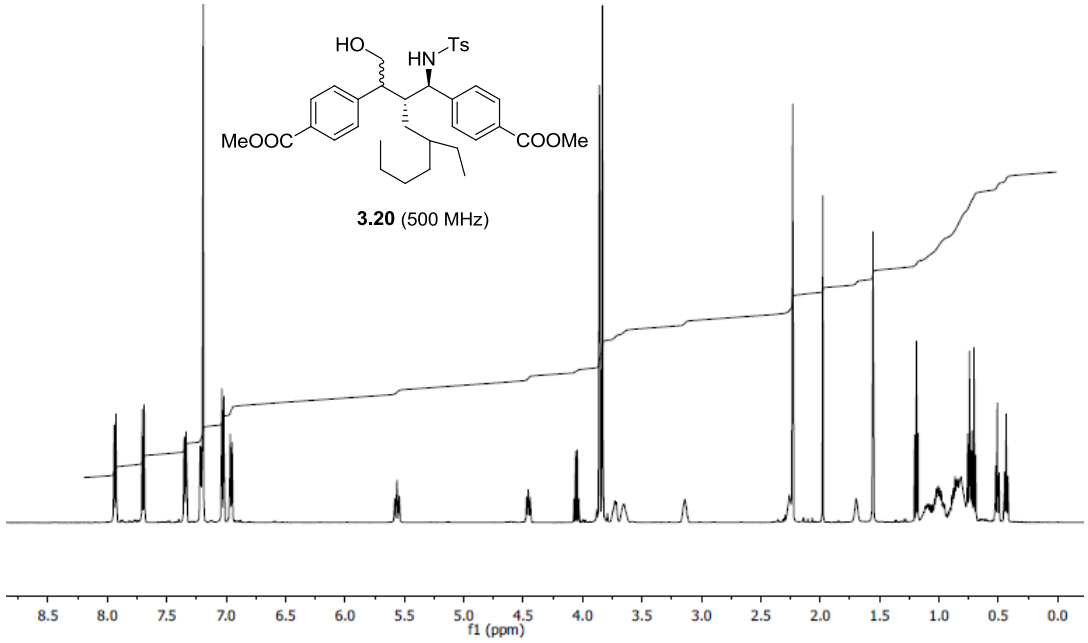

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
HN
Ts
MeOOC
n-hexyl
NO2

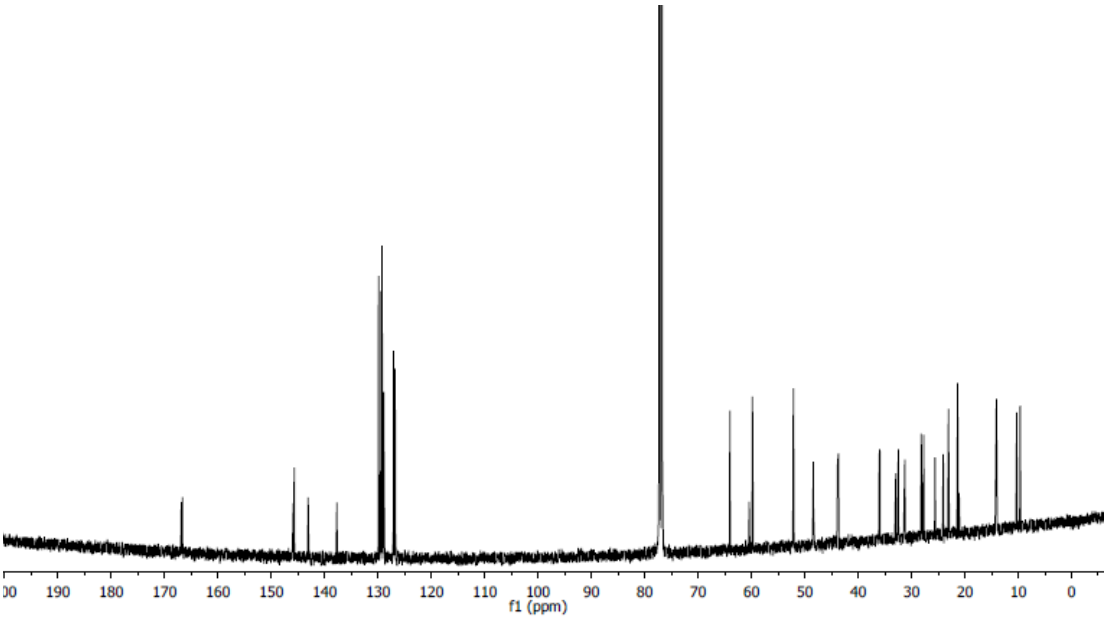
3.19 (500 MHz)

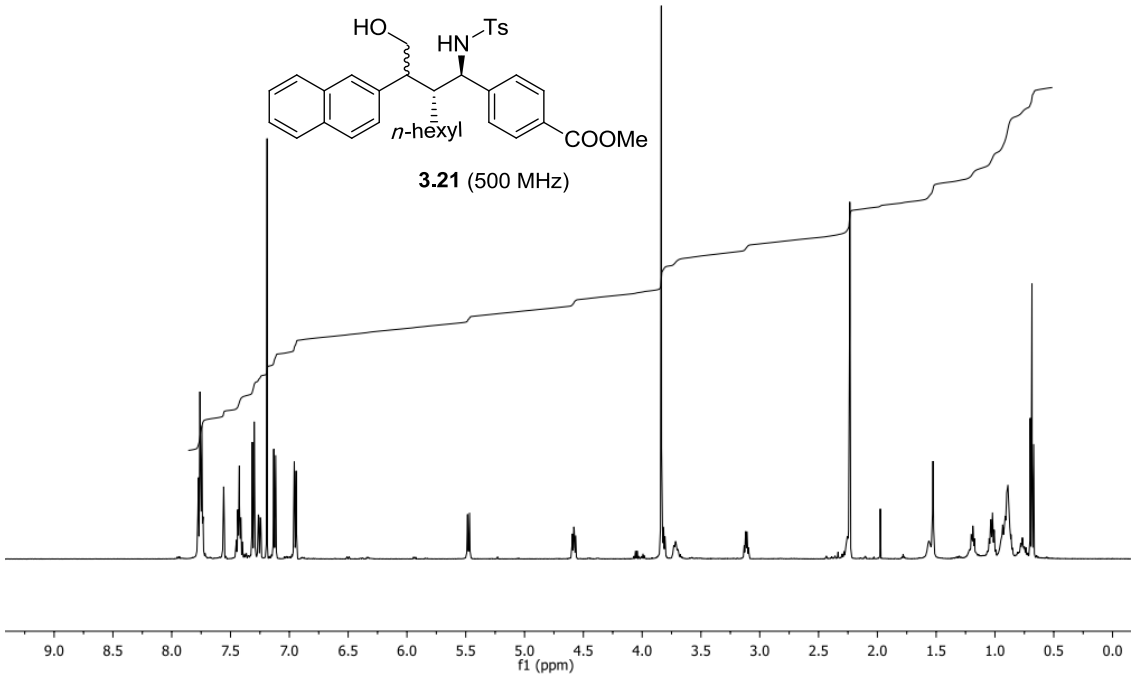
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

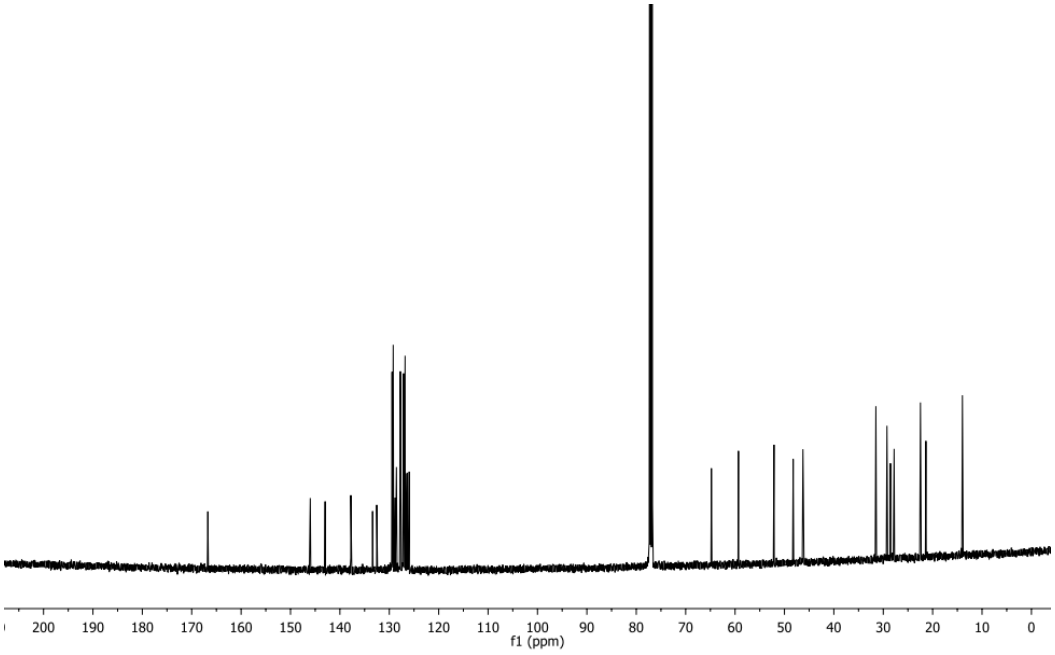

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

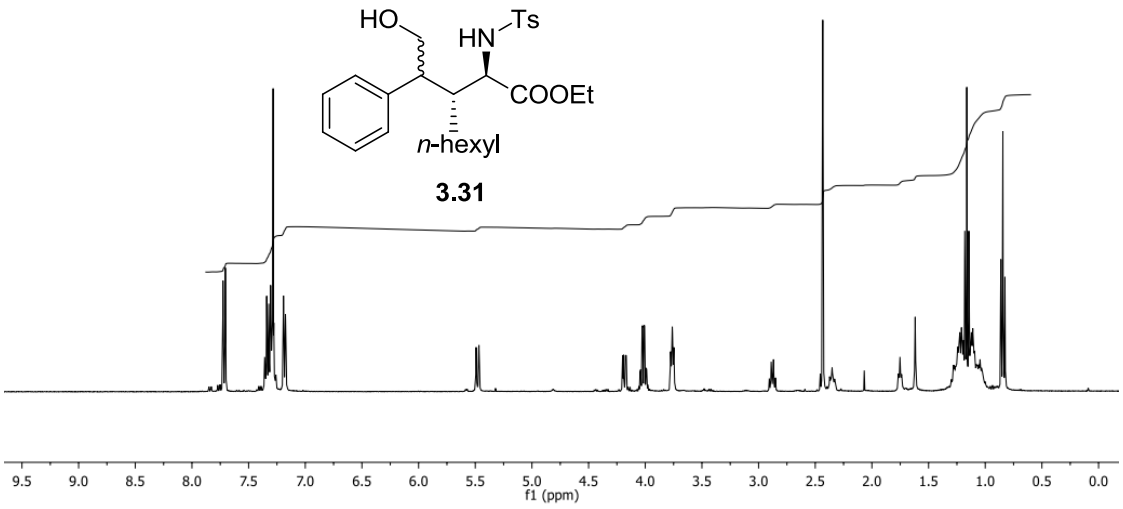

HO
HN
Ts
MeOOC
COOMe
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

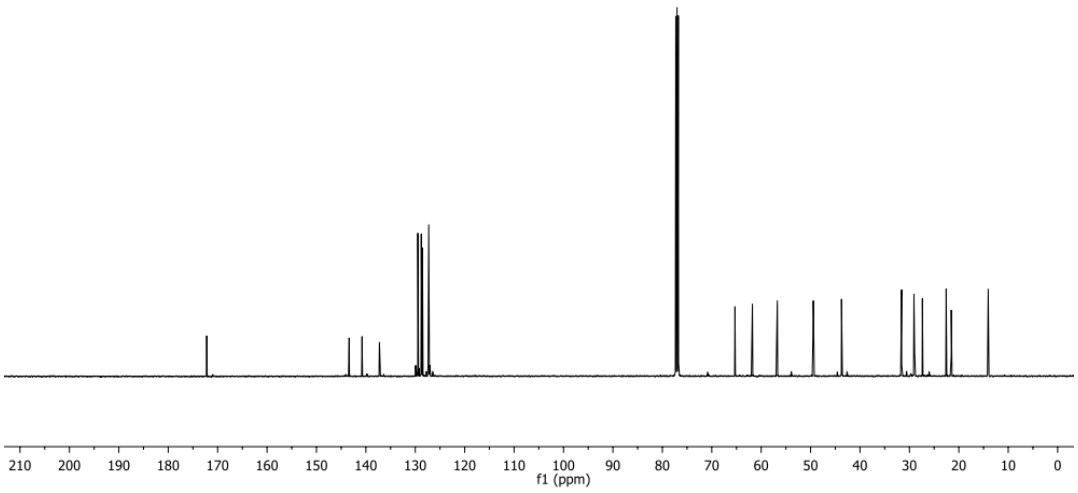
3.20 (500 MHz)

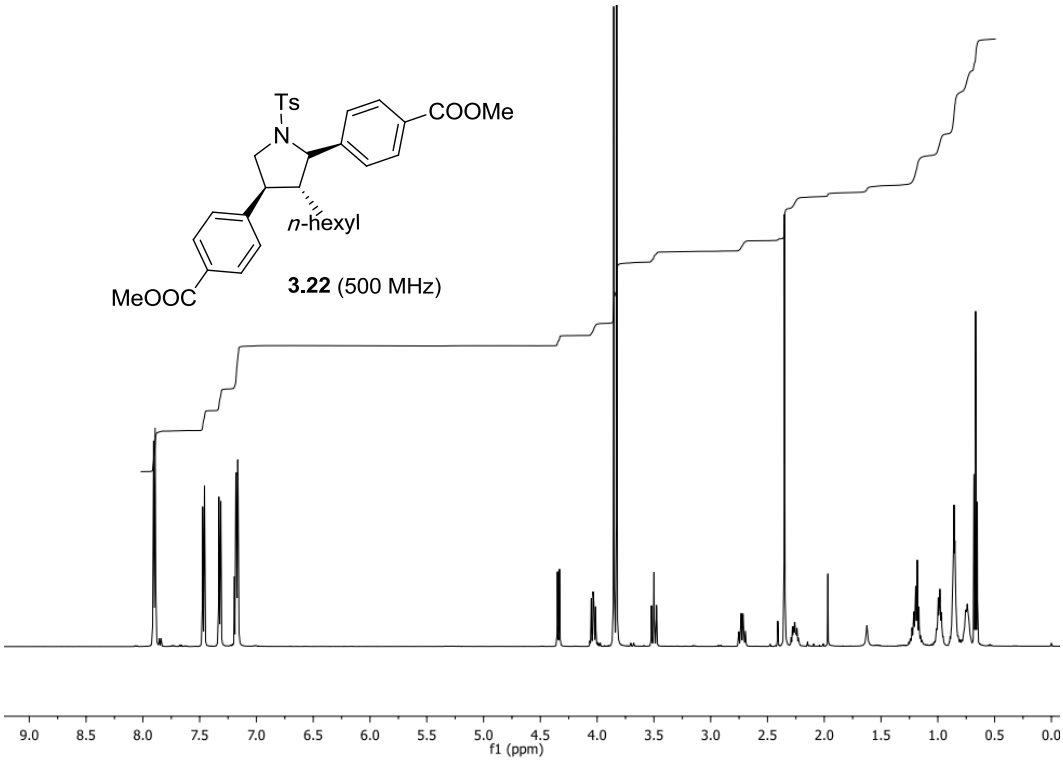

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

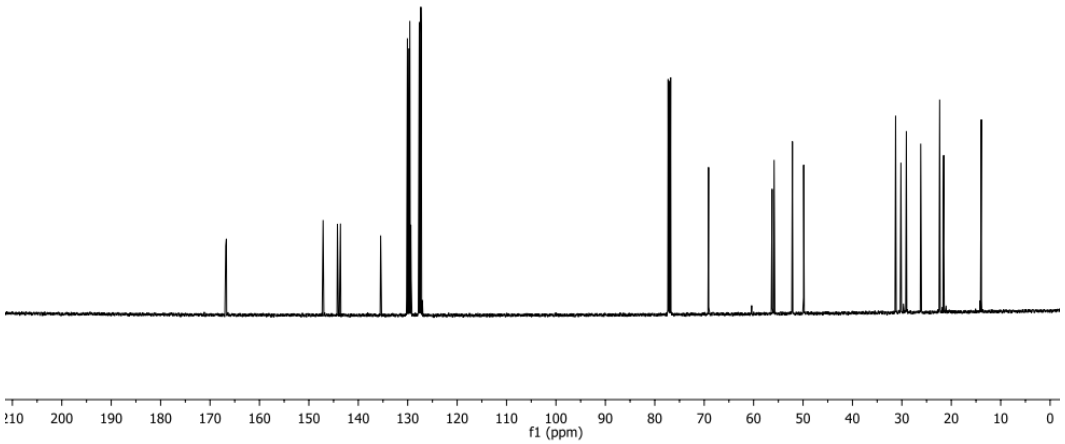

HO
HN
Ts
n-hexyl
COOMe
3.21 (500 MHz)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

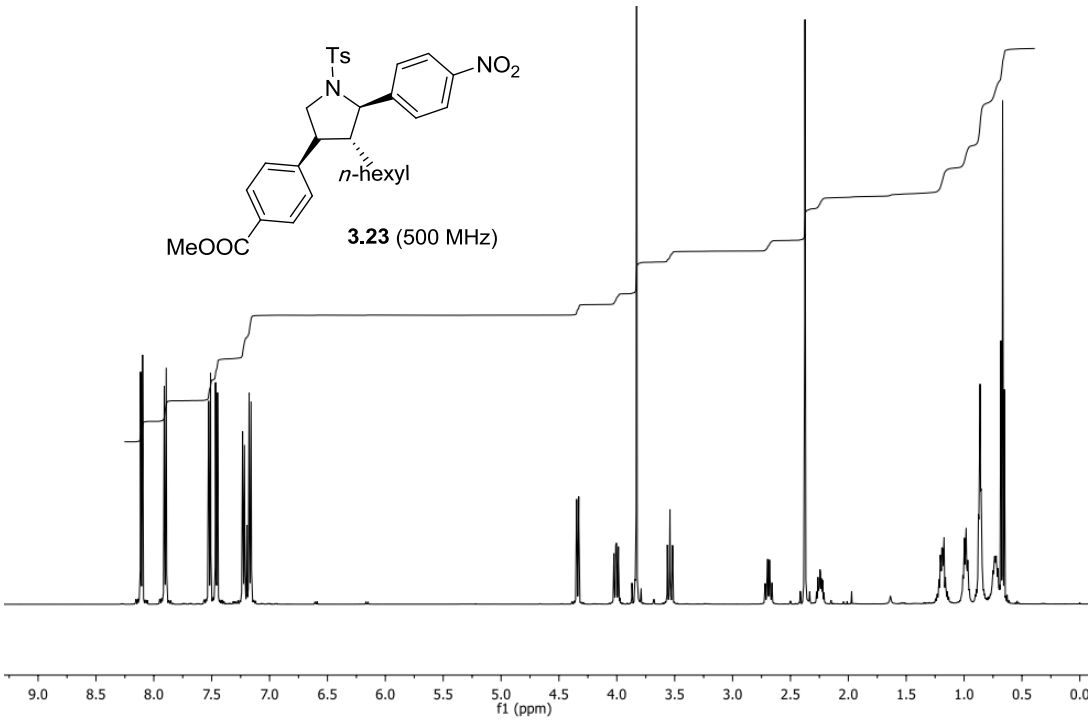

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

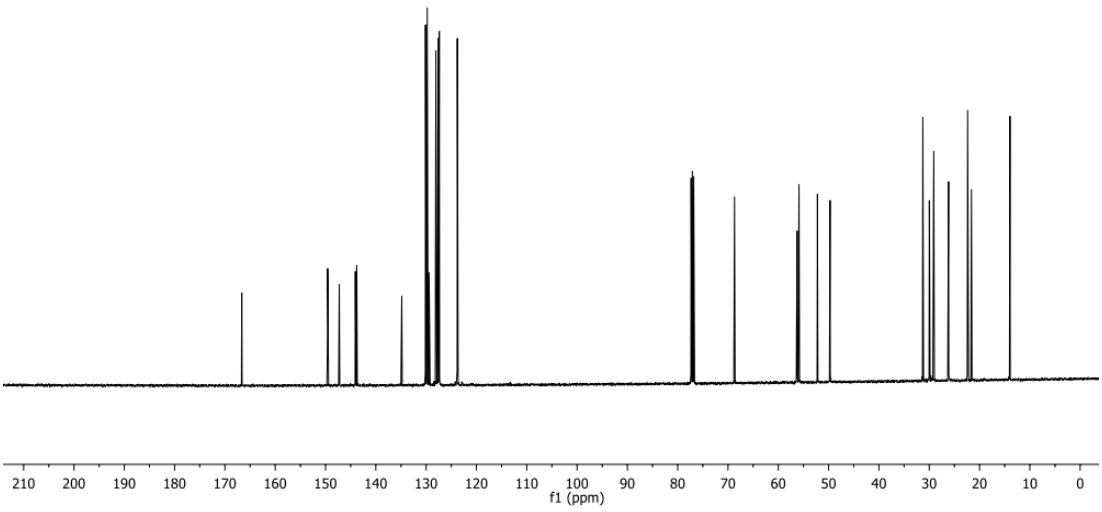

HO
HN
Ts
COOEt
n-hexyl
3.31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

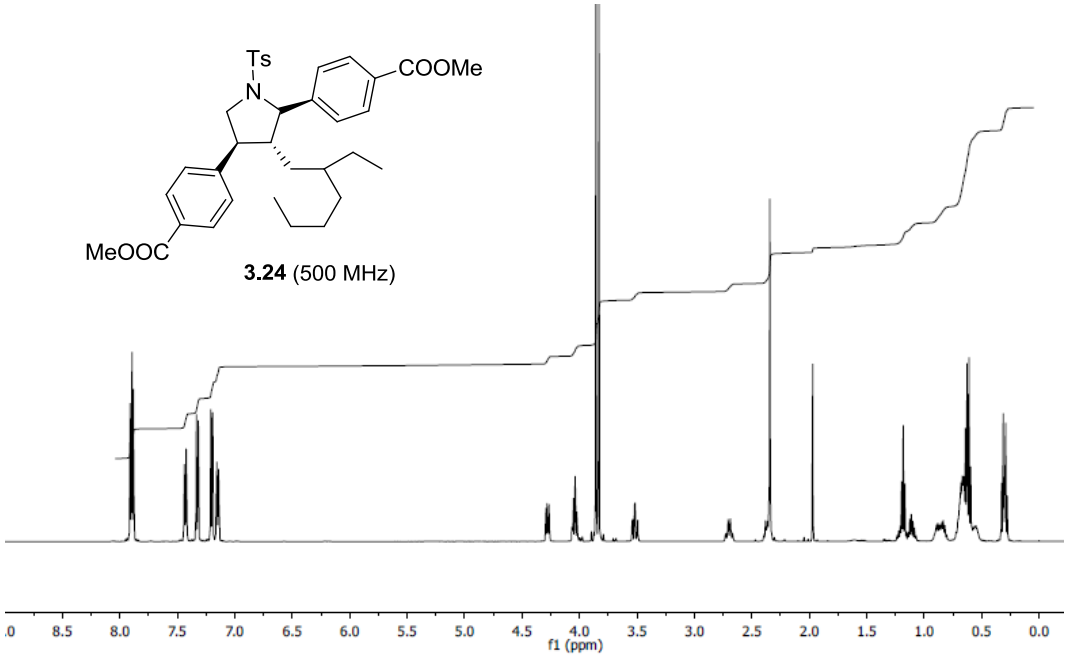

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ts
N
COOMe
n-hexyl
MeOOC
3.22 (500 MHz)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

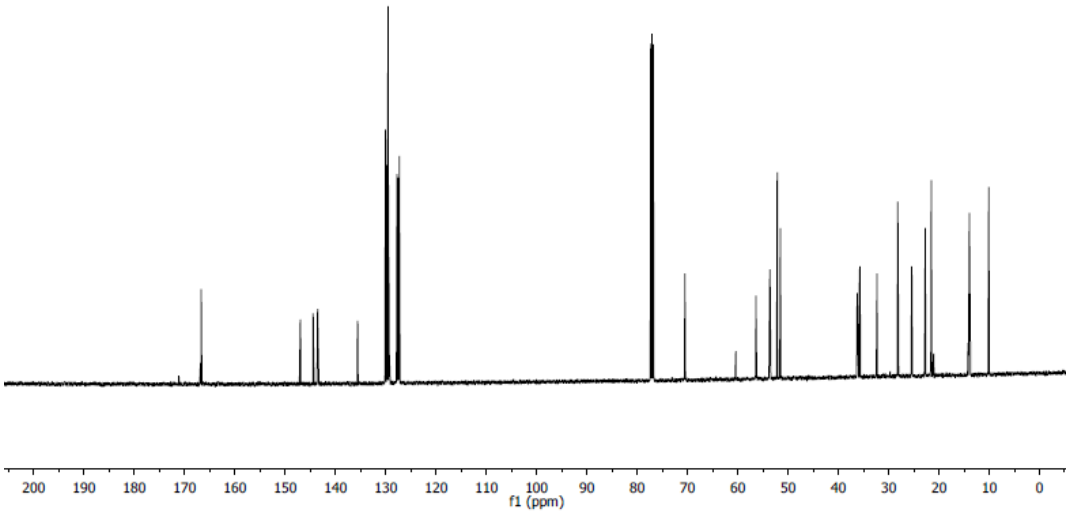

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

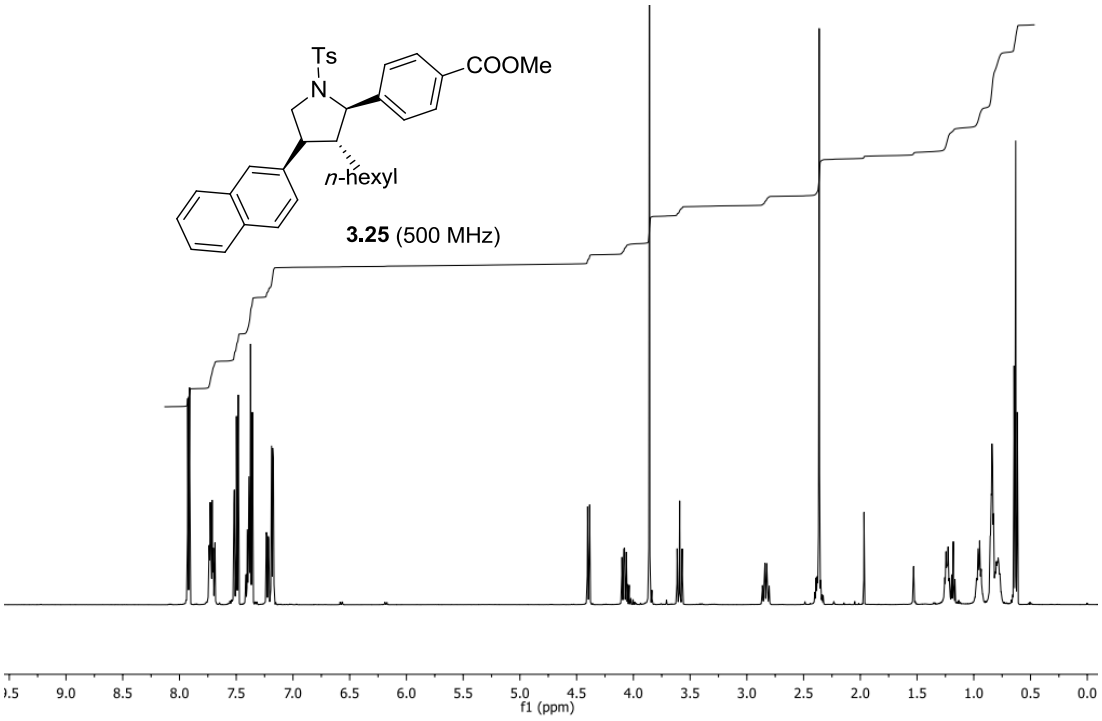

Ts
N
NO2
n-hexyl
MeOOC
3.23 (500 MHz)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

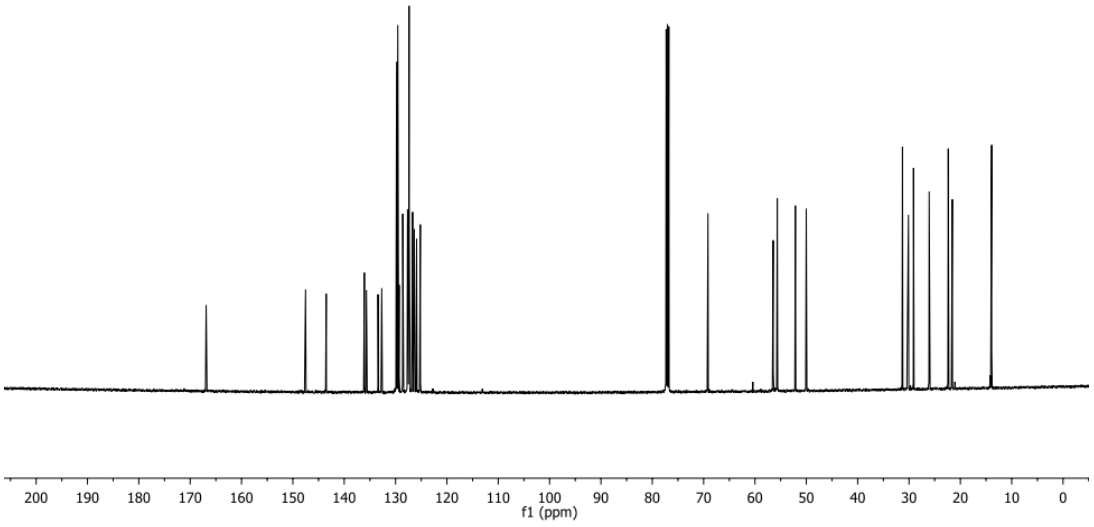

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

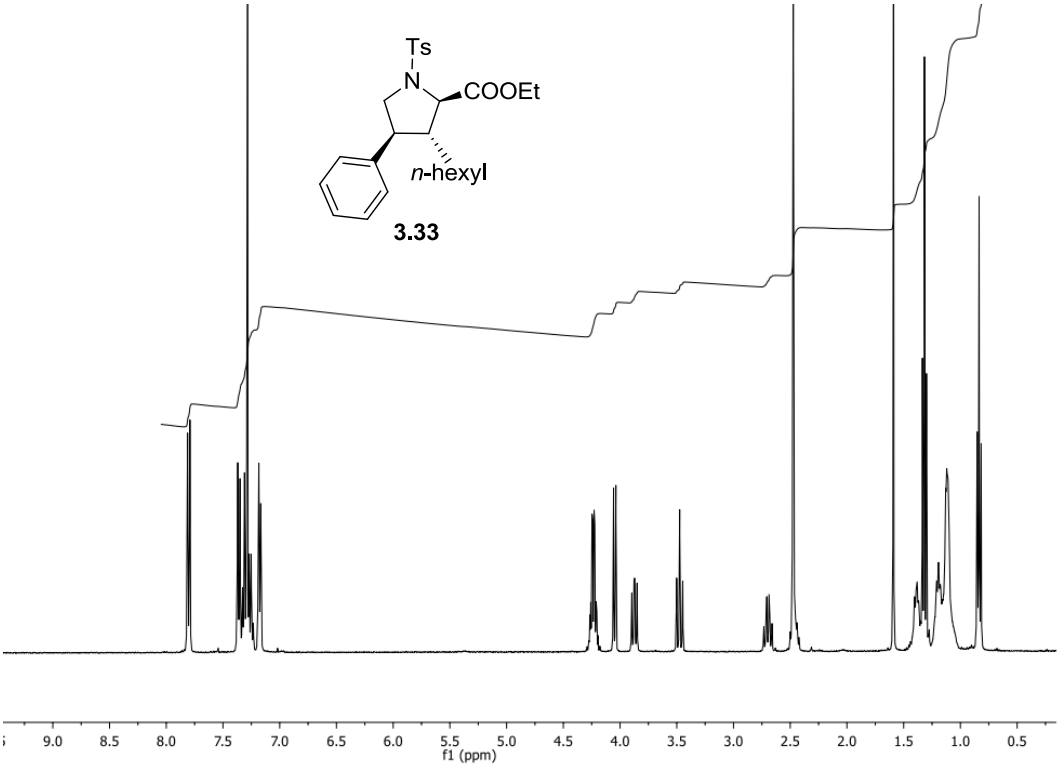


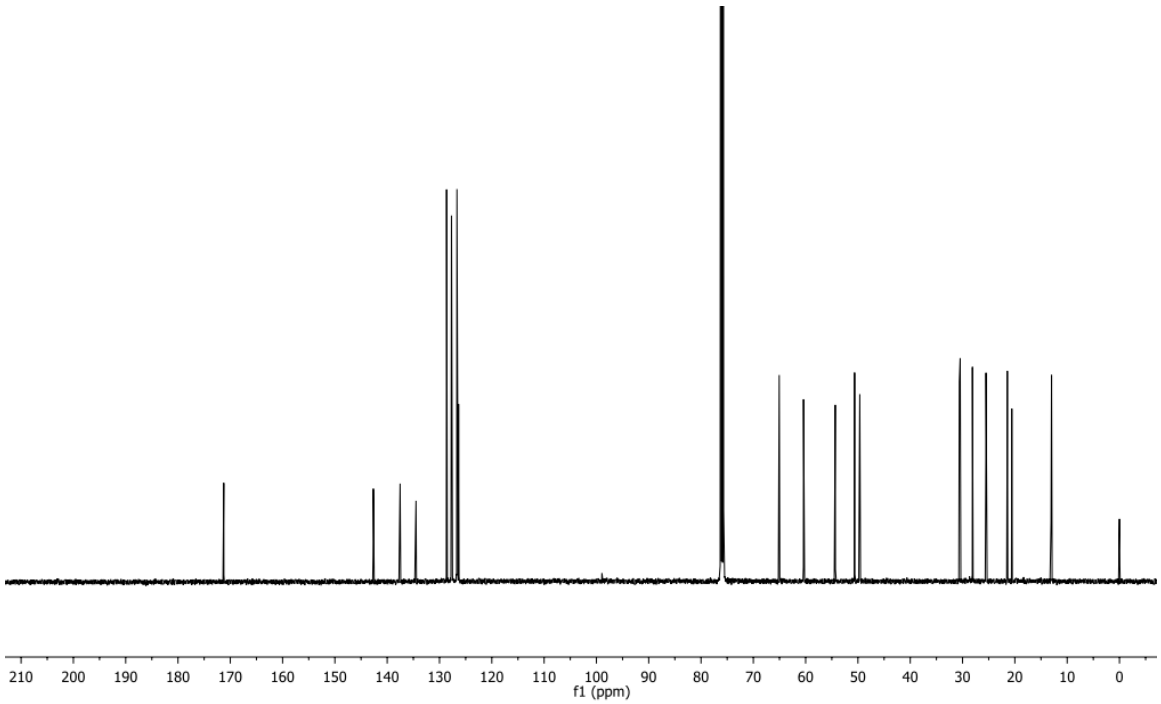
3.24 (500 MHz)

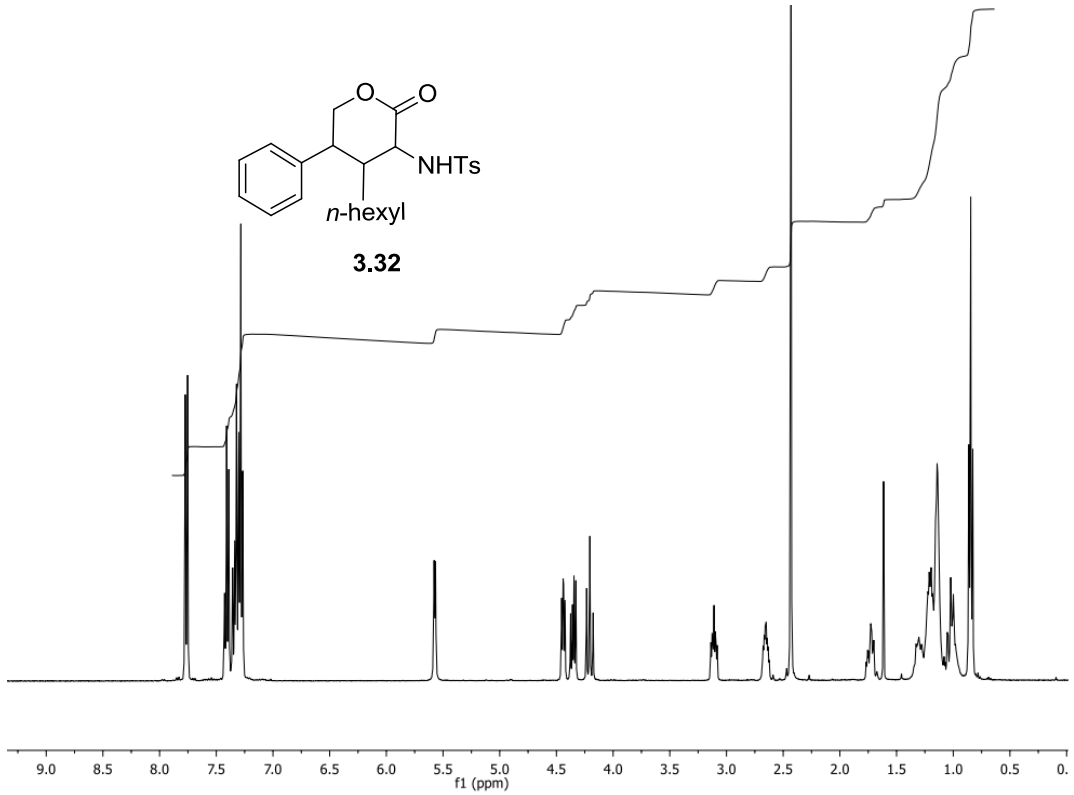


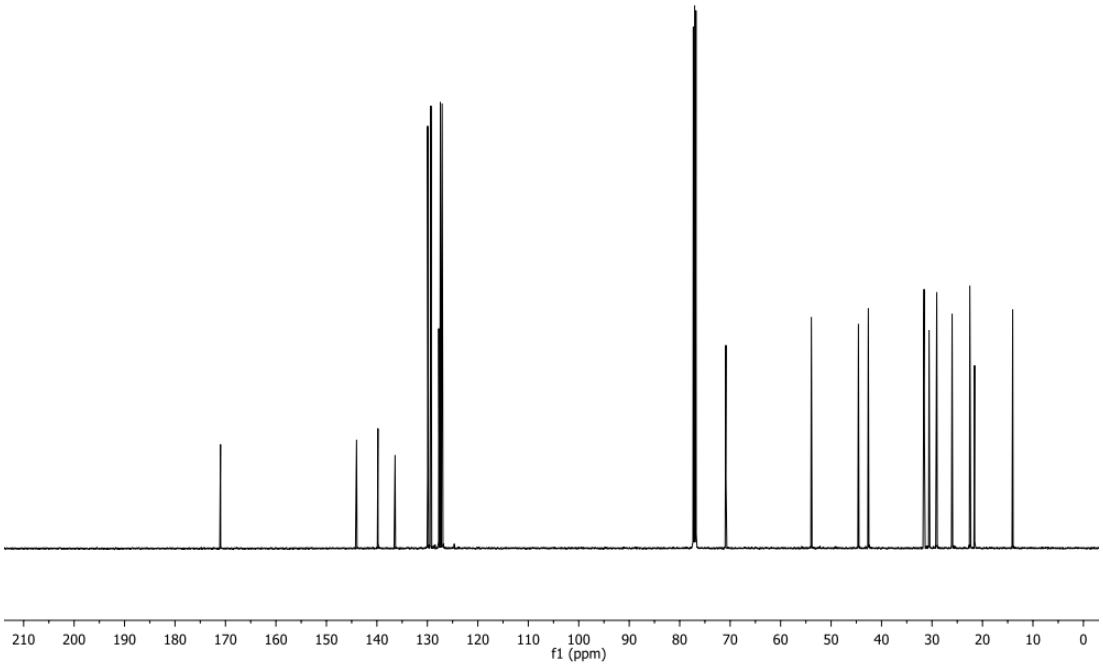

Ts
N
COOMe
n-hexyl
3.25 (500 MHz)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

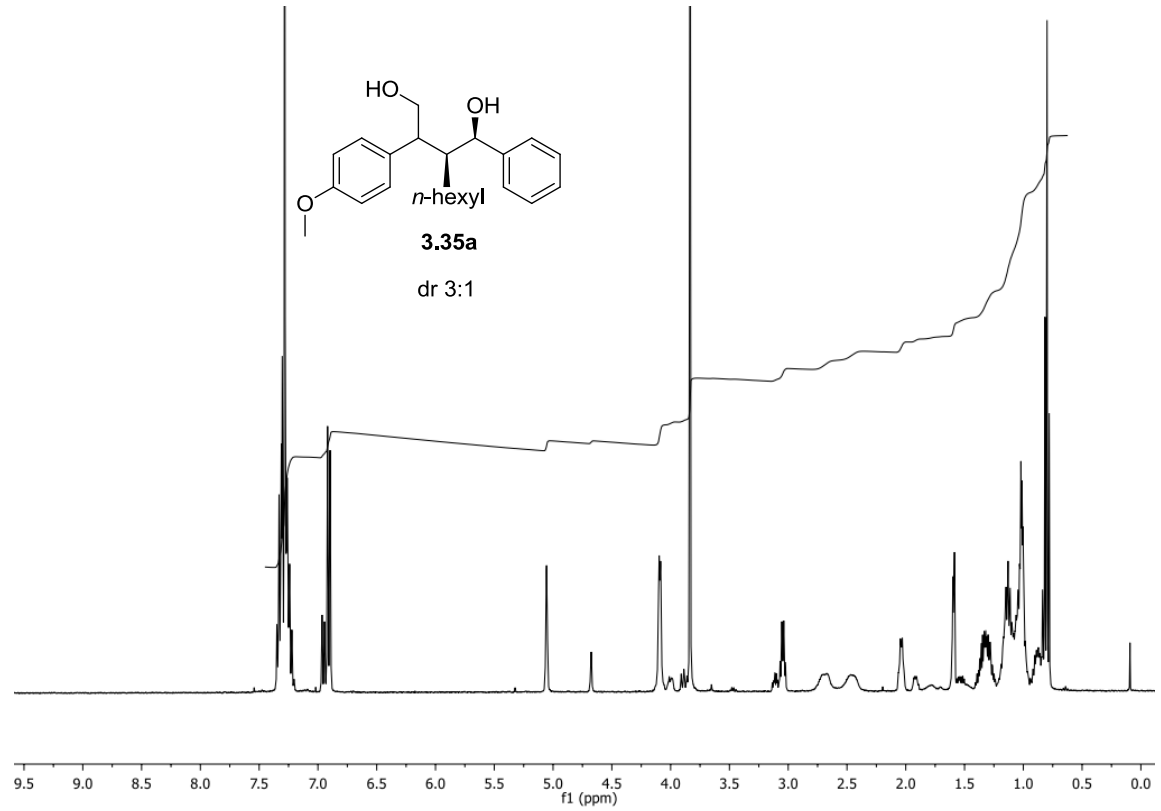

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

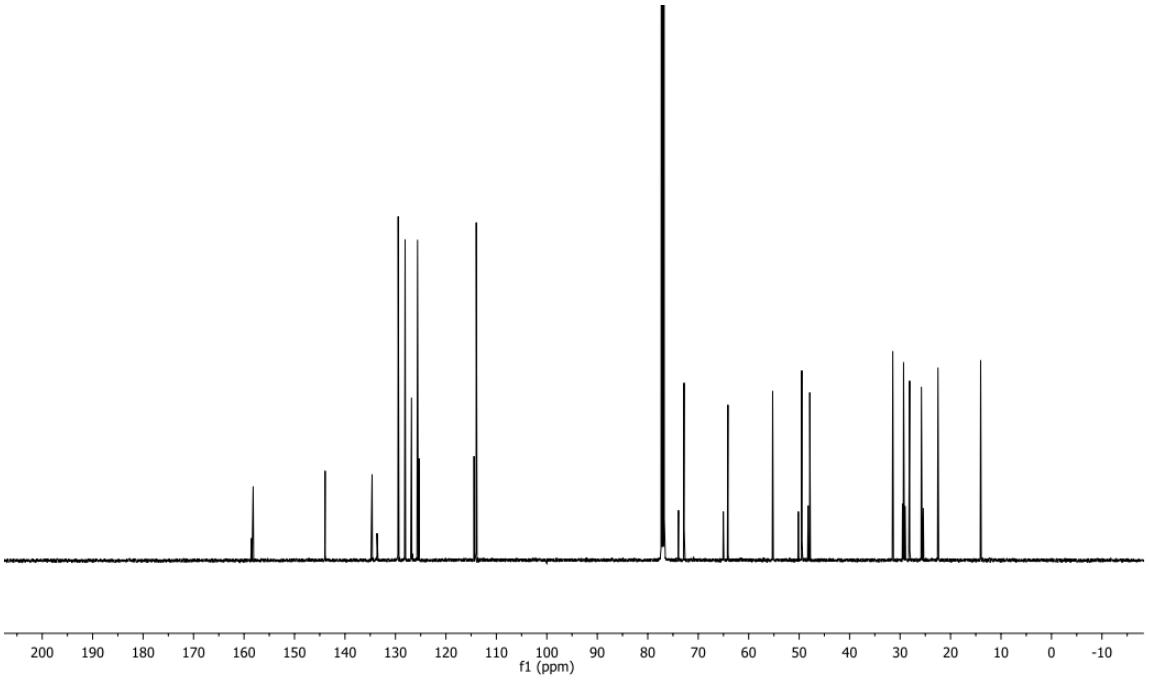

Ts
N
COOEt
n-hexyl
3.33
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

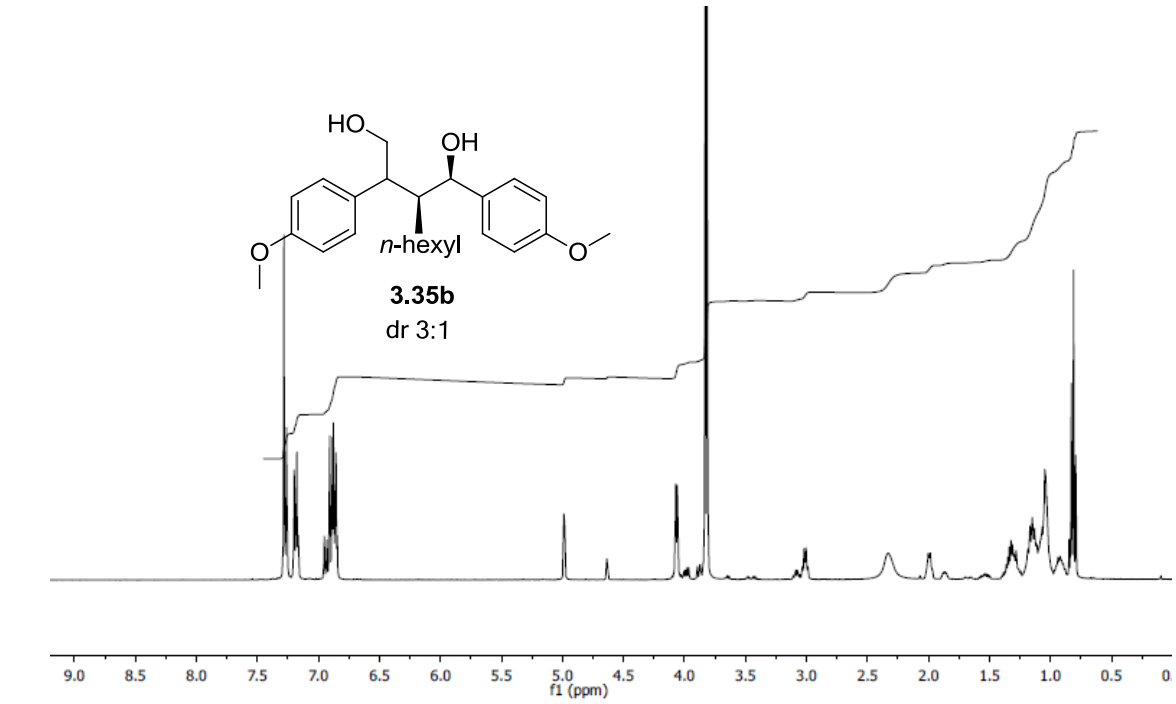

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

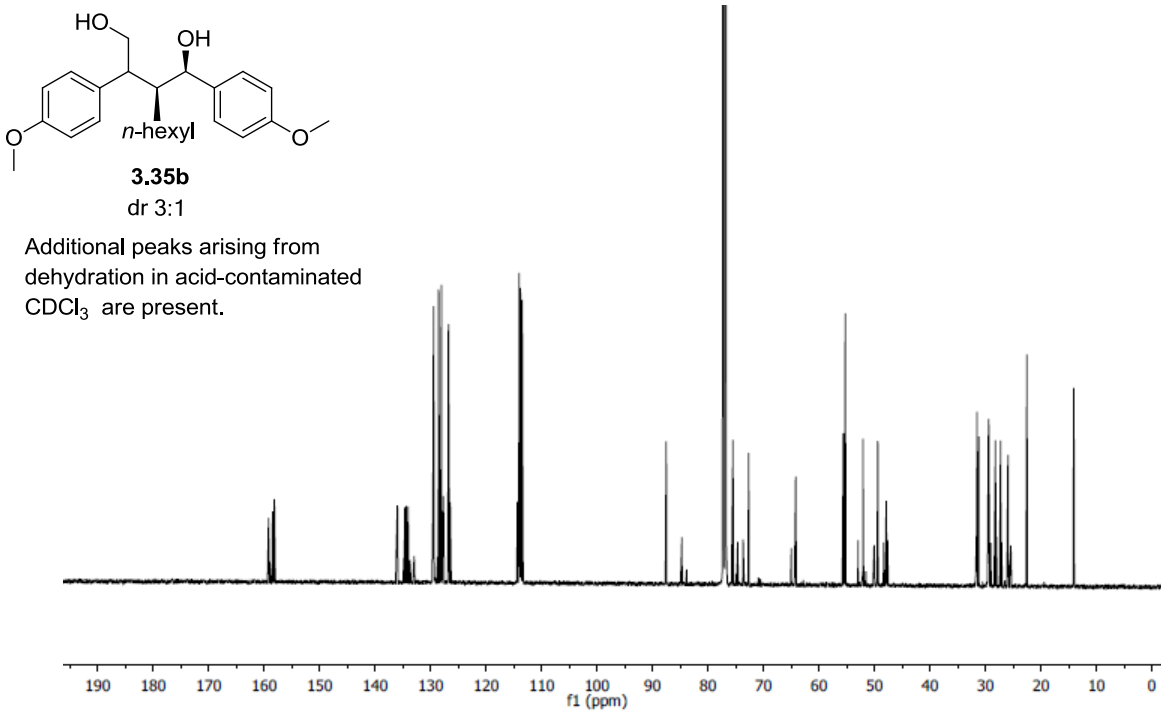

O
O
NHTs
n-hexyl
3.32
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

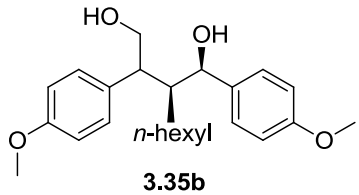

HO
OH
O
n-hexyl
3.35a
dr 3:1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)





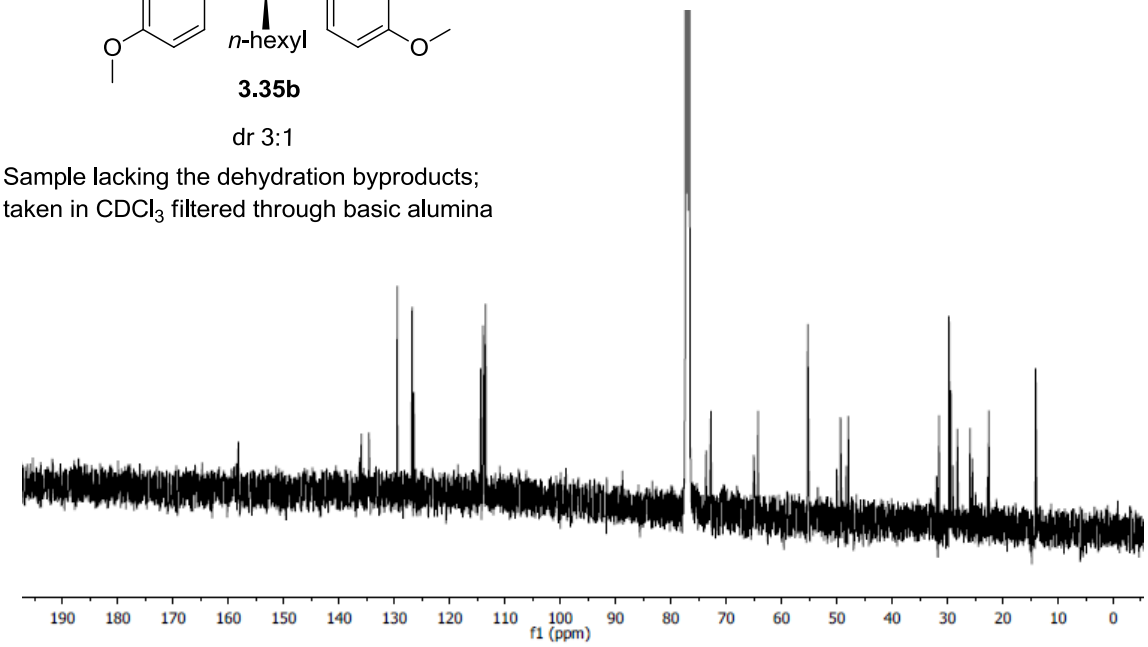
Additional peaks arising from dehydration in acid-contaminated $CDCl_3$ are present.

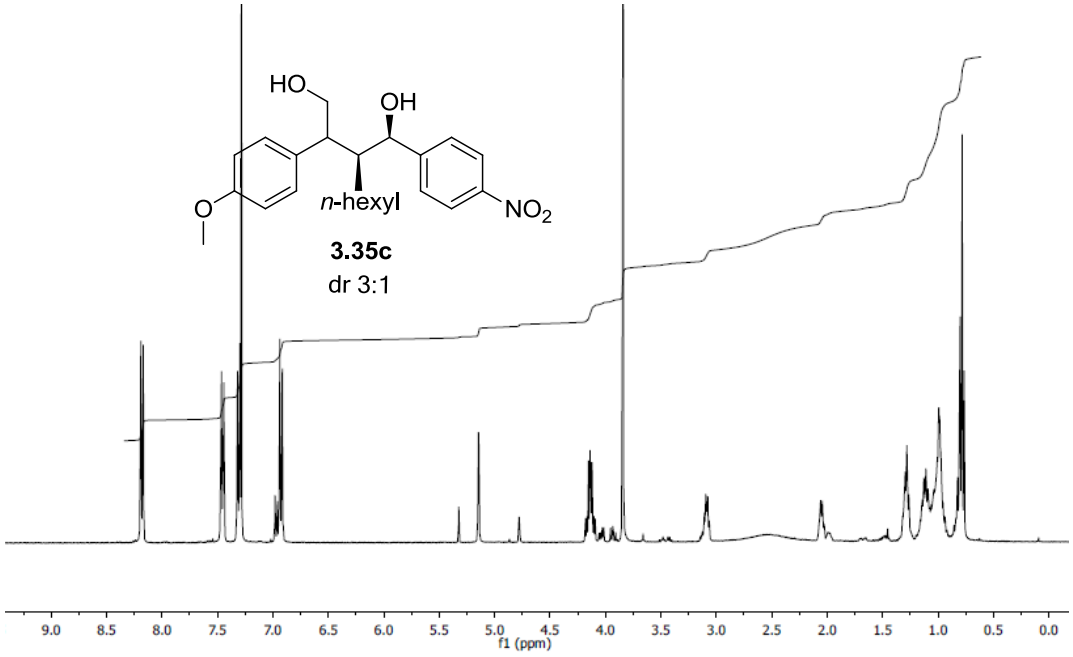


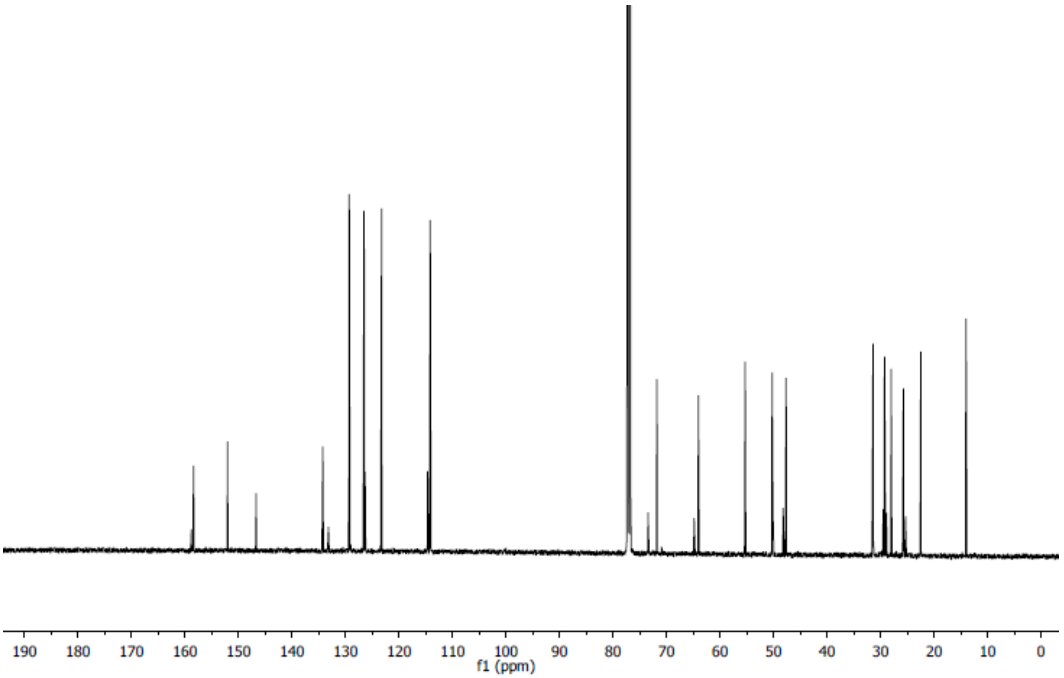
3.35b

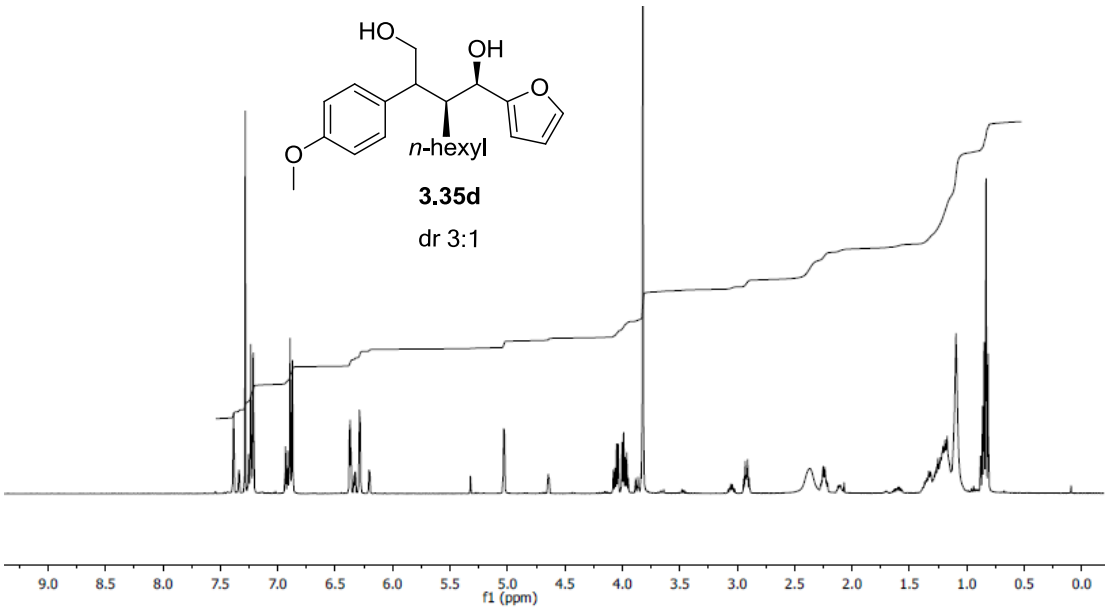
dr 3:1

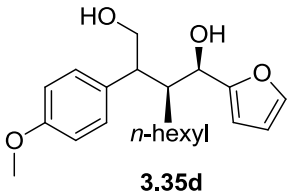
Sample lacking the dehydration byproducts; taken in $CDCl_3$ filtered through basic alumina




HO
OH
O
n-hexyl
NO2
3.35c
dr 3:1
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

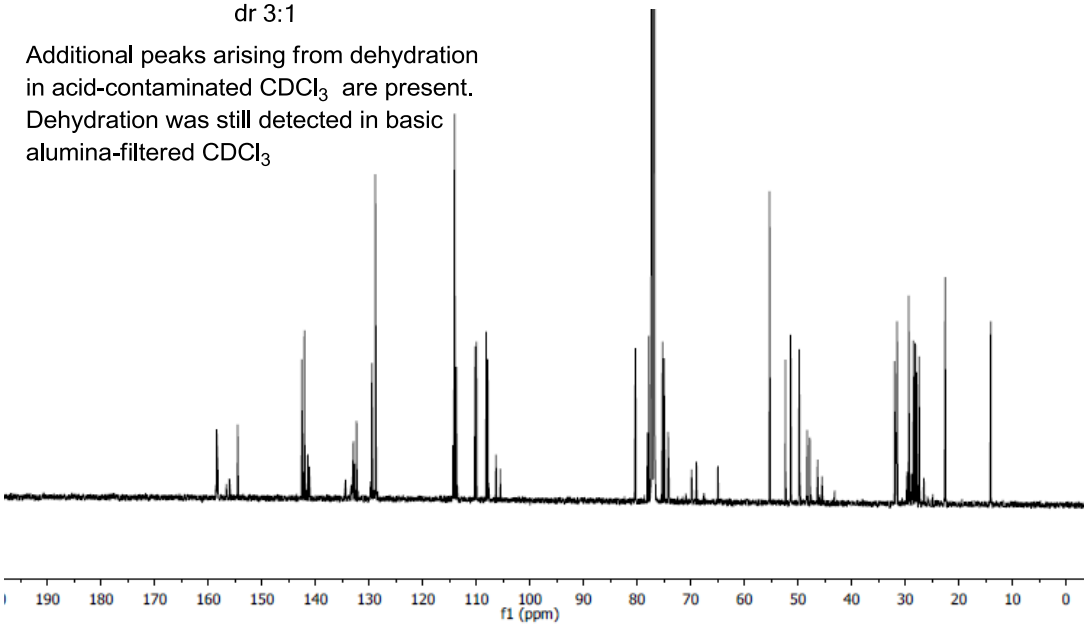


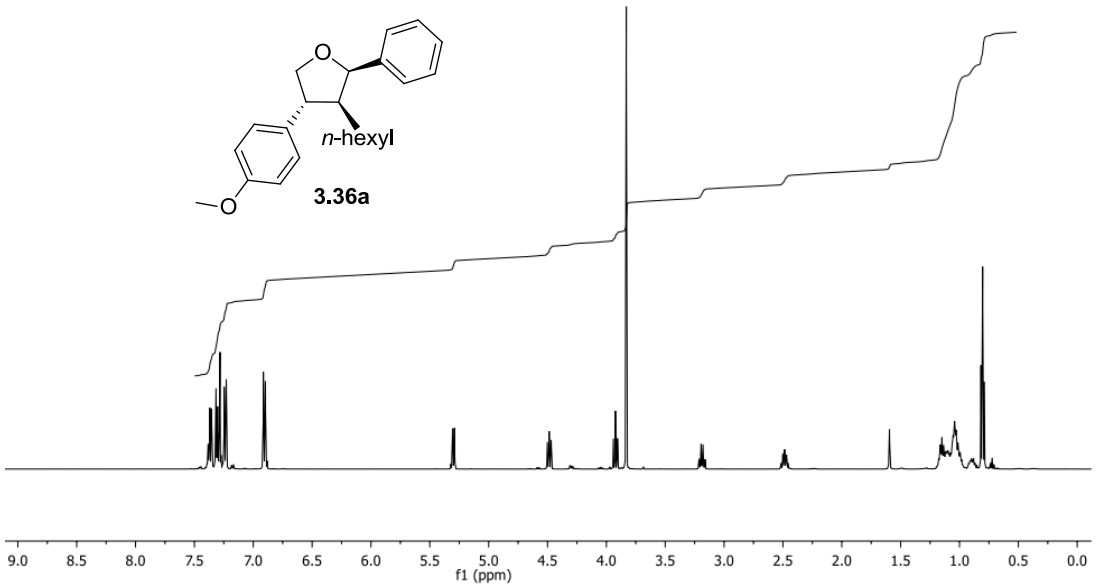


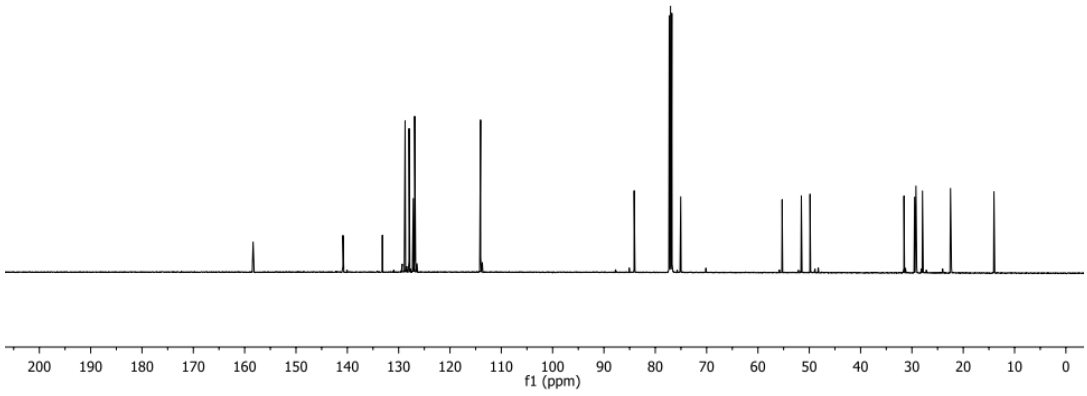
3.35d

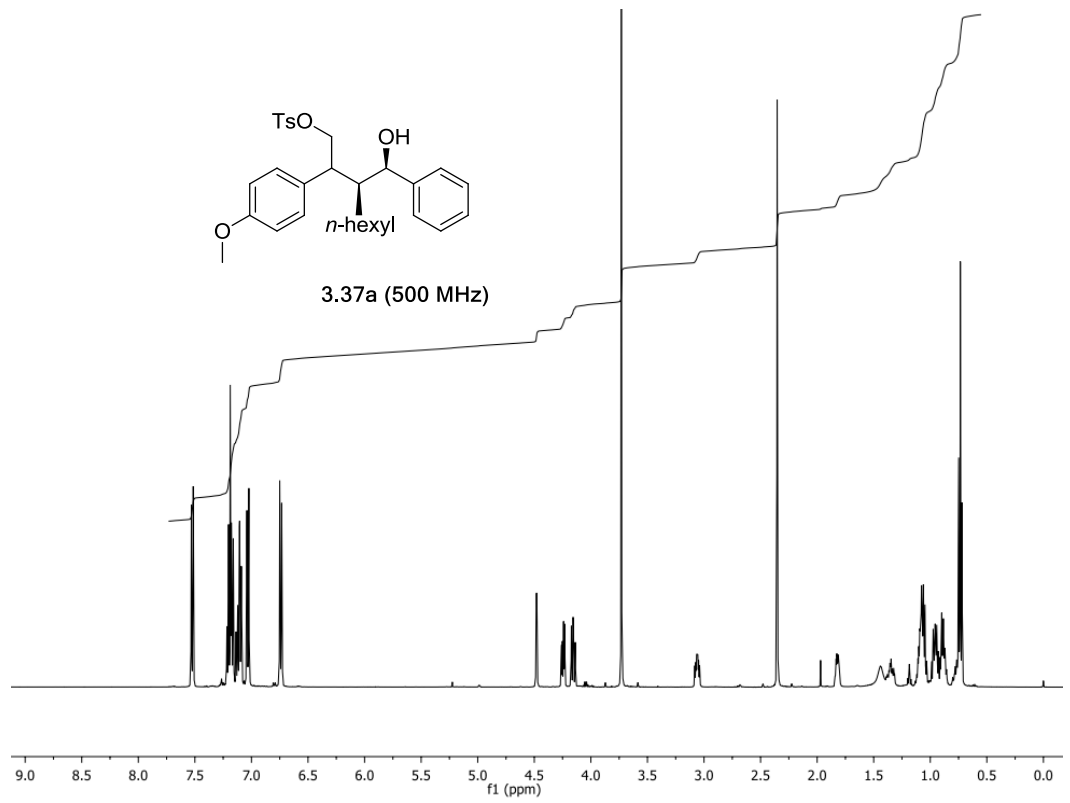
dr 3:1

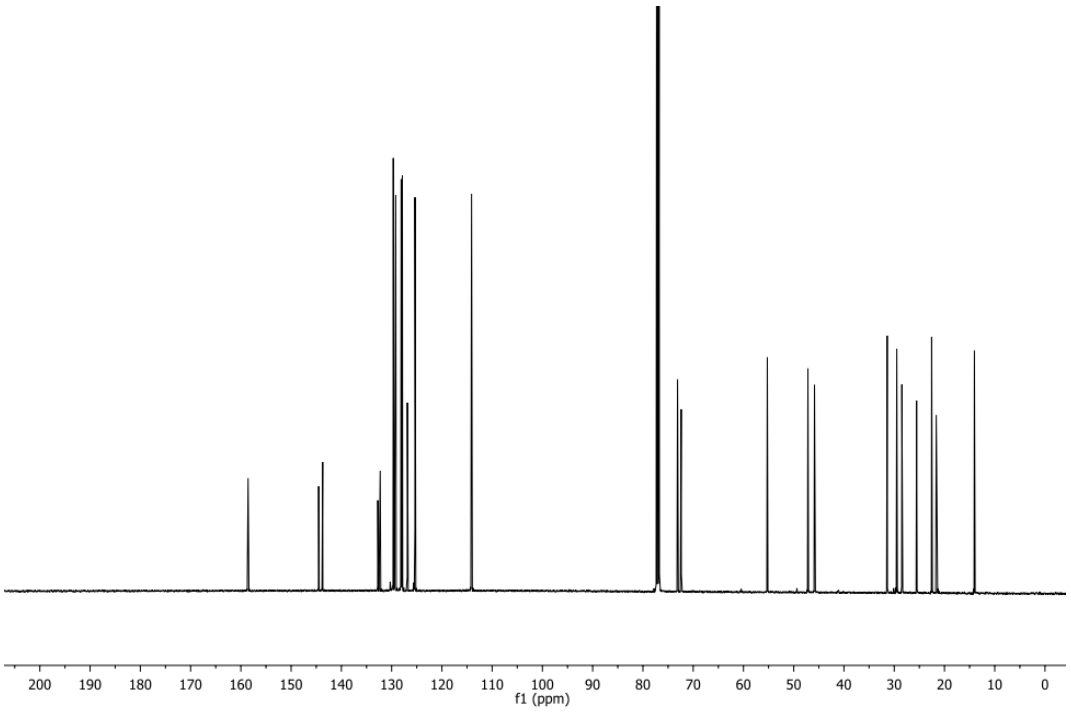
Additional peaks arising from dehydration in acid-contaminated $CDCl_3$ are present. Dehydration was still detected in basic alumina-filtered $CDCl_3$

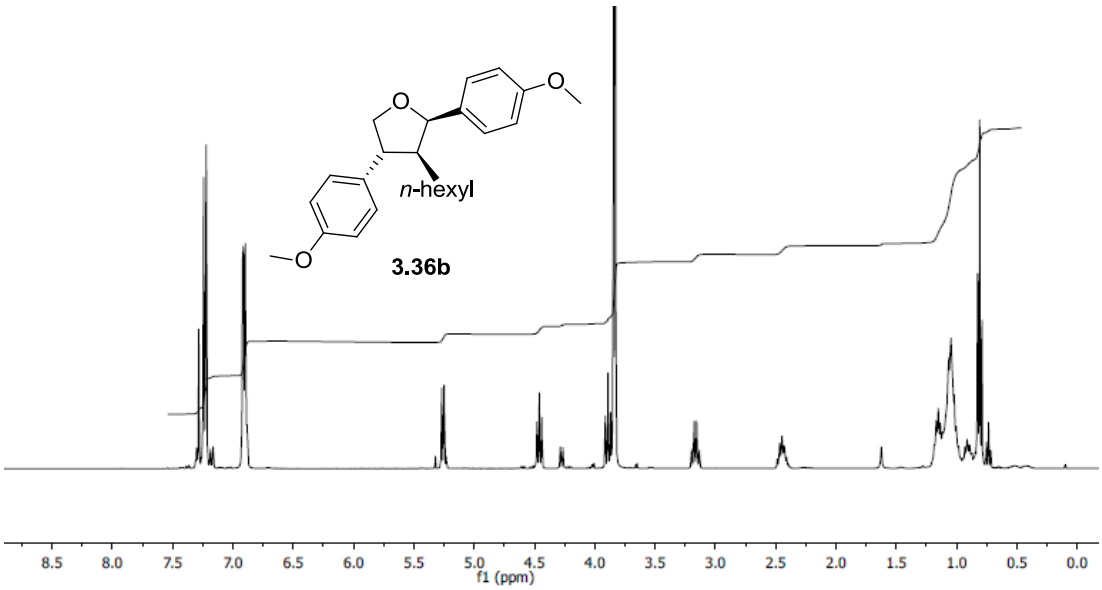


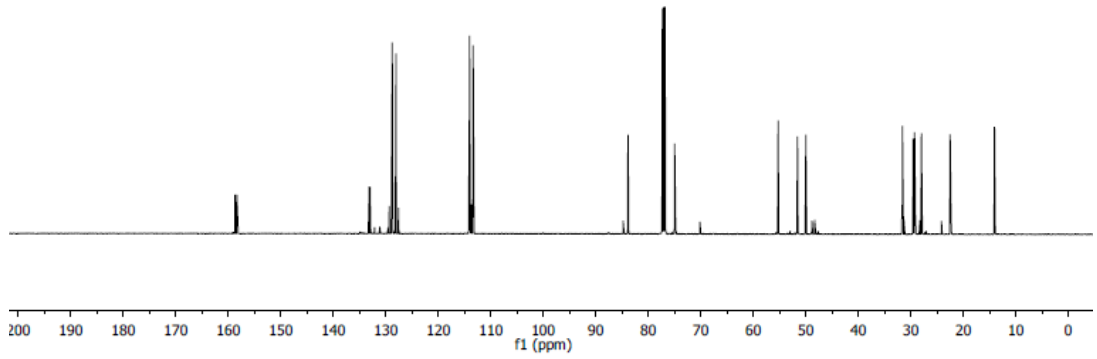

O
n-hexyl
O
3.36a
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

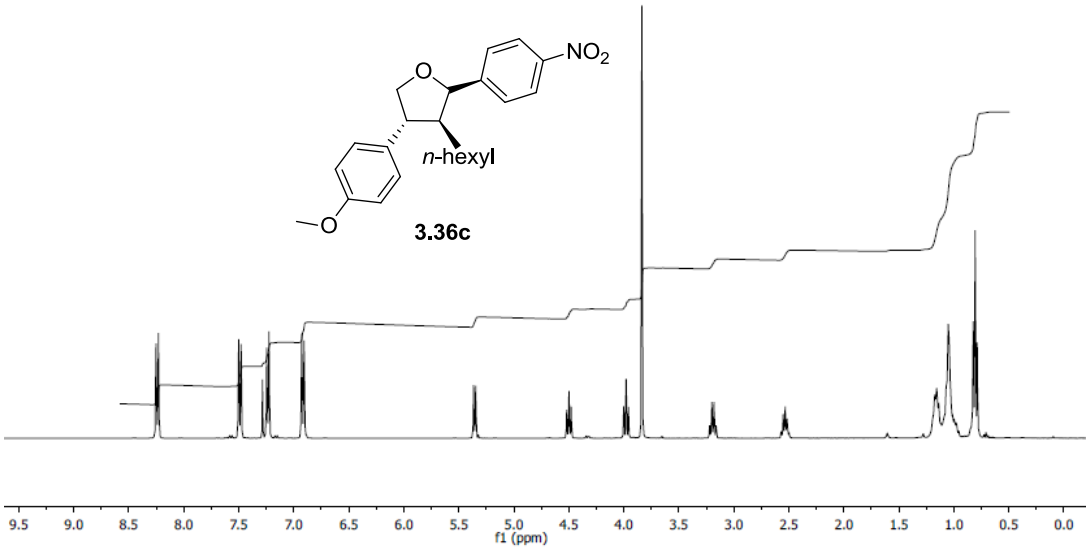

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

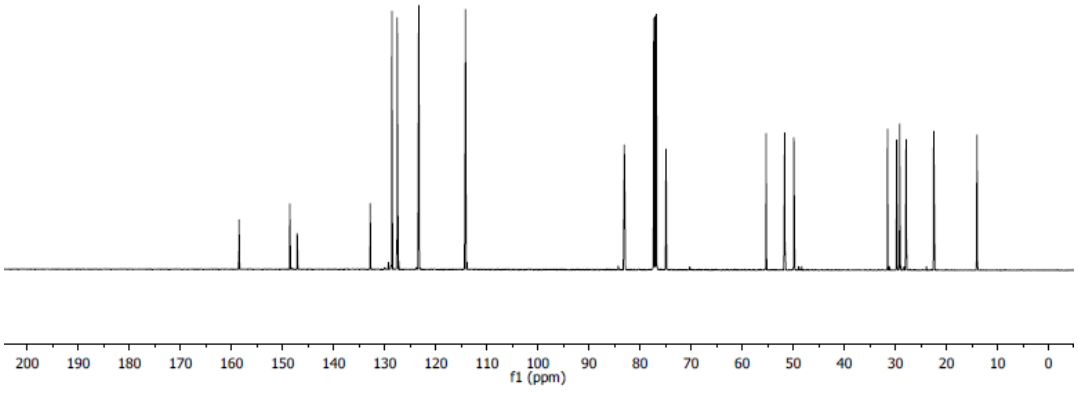

TsO
OH
n-hexyl
O
3.37a (500 MHz)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

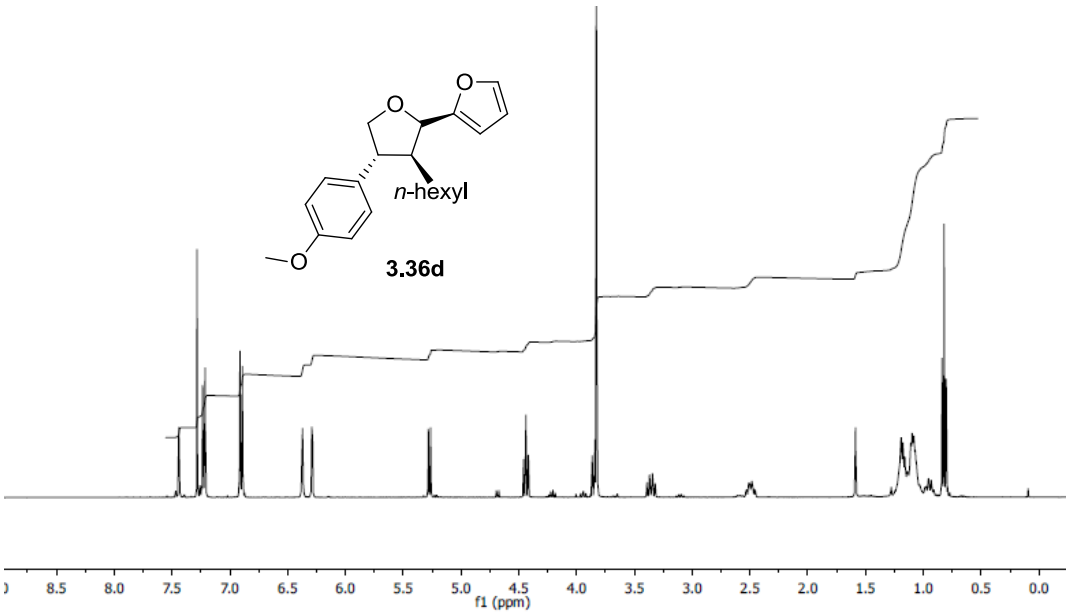

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

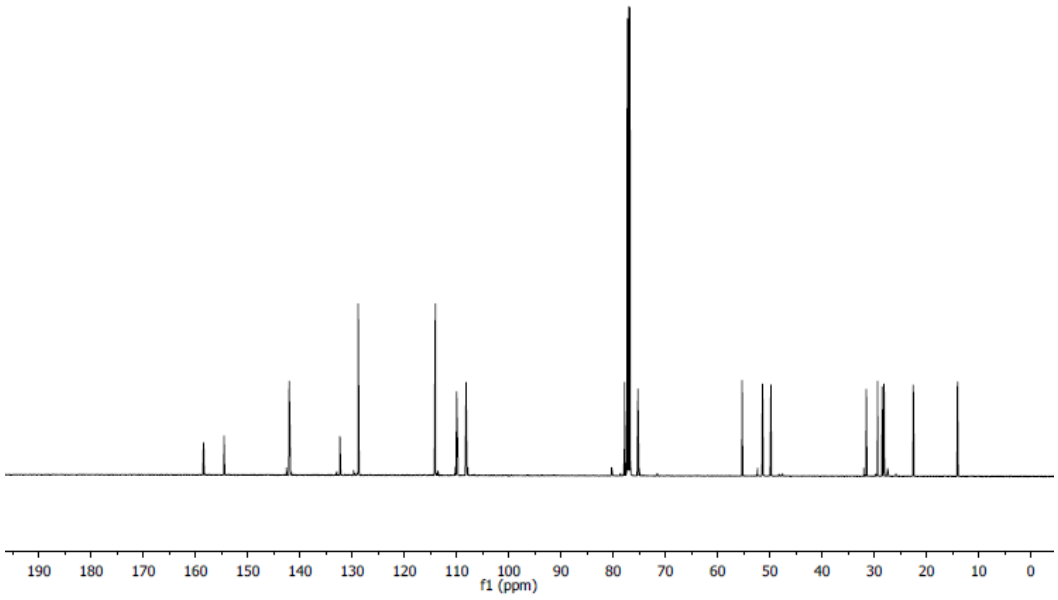

O
O
n-hexyl
O
3.36b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NO2
O
n-hexyl
O
3.36c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

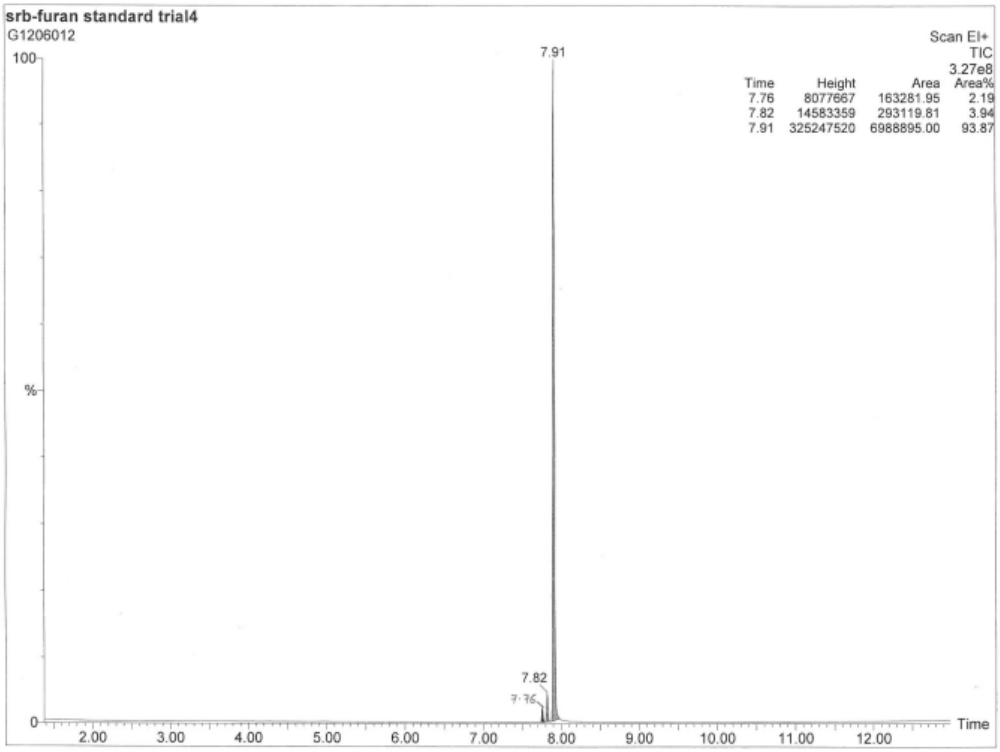

O
O
n-hexyl
O
3.36d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

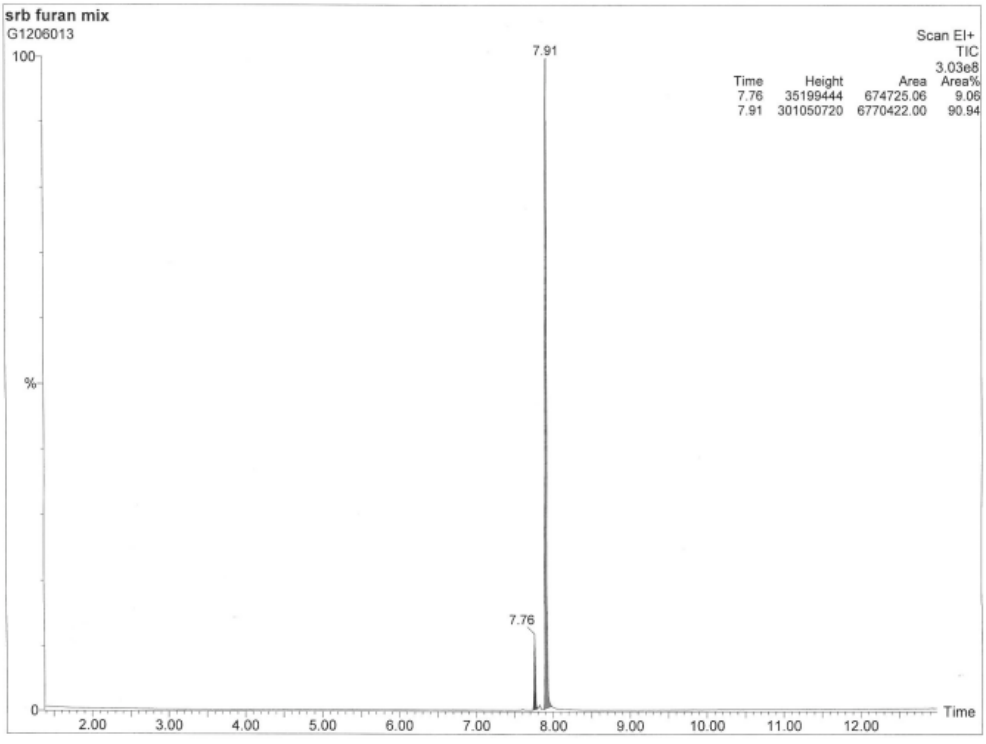

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

GC Analysis of 9:1 mixture of 3.36a

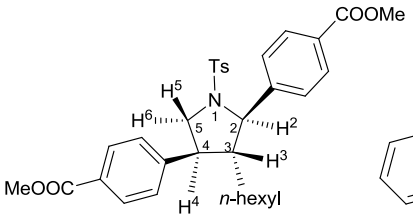
The GCMS data were collected on an Agilent 6890N gas chromatograph eluting into a Quattro Micro GC mass spectrometer (Micromass Ltd, Manchester UK). An HP-5MS, 15 meter column with a 0.25 ID was used. The carrier gas was Helium using constant flow control set to 1.5 mL per minute. 1.0µl of sample was injected into the column with a 20:1 split ratio. The injector port temperature was 240^{o}C. The chromatographic conditions were as follows: The initial column temperature was 50^{o}C with a 1 minute hold after which the temperature was increased 25^{o}C/min to a final temperature of 300^{o}C and held for 2 minutes. EI ionization was used with ion energy of 70V. The mass range was 45 to 400 m/z with a 0.3 scan time and an inter scan delay time of 0.07 seconds.

The first spectra is of the single diastereomer (**3.36a**) and second is of the 9:1 diastereomeric mixture (**3.36a**)


srb-furan standard trial4
G1206012
Scan EI+
TIC
3.27e8
Time Height Area Area%
7.76 8077667 163281.95 2.19
7.82 14583359 293119.81 3.94
7.91 325247520 6988895.00 93.87
7.91
7.82
7.76
100
%
0
2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00 11.00 12.00
Time


srb furan mix
G1206013
Scan EI+
TIC
3.03e8
Time Height Area Area%
7.76 35199444 674725.06 9.06
7.91 301050720 6770422.00 90.94
7.91
7.76
100
%
0
2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00 11.00 12.00
Time

HSQC ^{13}C - ^{1}H correlation data for 3.22, 3.33 and 3.36a



3.22 Correlations found

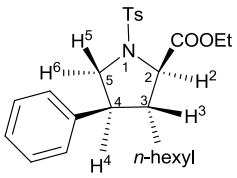
All the values are in ppm

C_2 (69.1) - H^2 (4.42)

C_3 (55.8) - H^3 (2.33)

C_4 (49.8) - H^4 (2.80)

C_5 (56.2) - H^5 and H^6 (4.11 / 3.57)



3.33 Correlations found

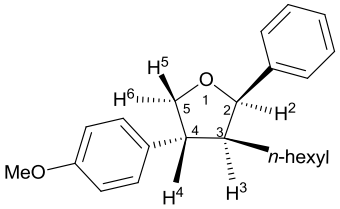
All the values are in ppm

C_2 (66.0) - H^2 (4.05)

C_3 (51.6) - H^3 (2.46)

C_4 (50.7) - H^4 (2.70)

C_5 (55.3) - H^5 and H^6 (3.87 / 3.48)



3.36a Correlations found

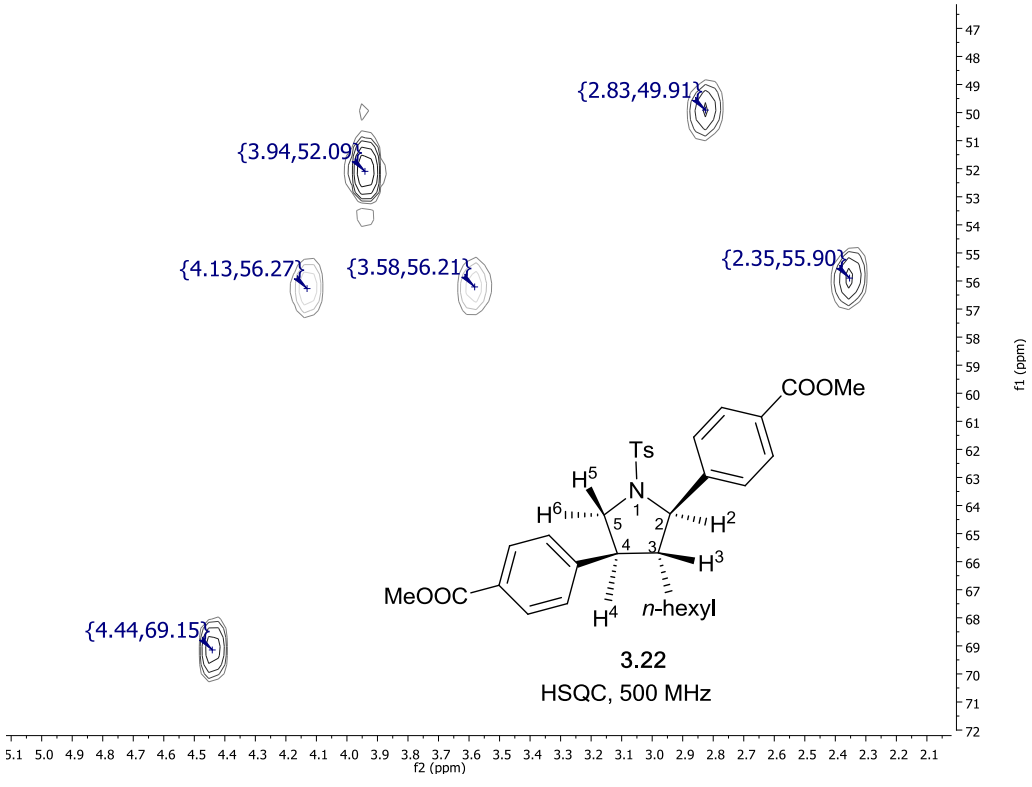
All the values are in ppm

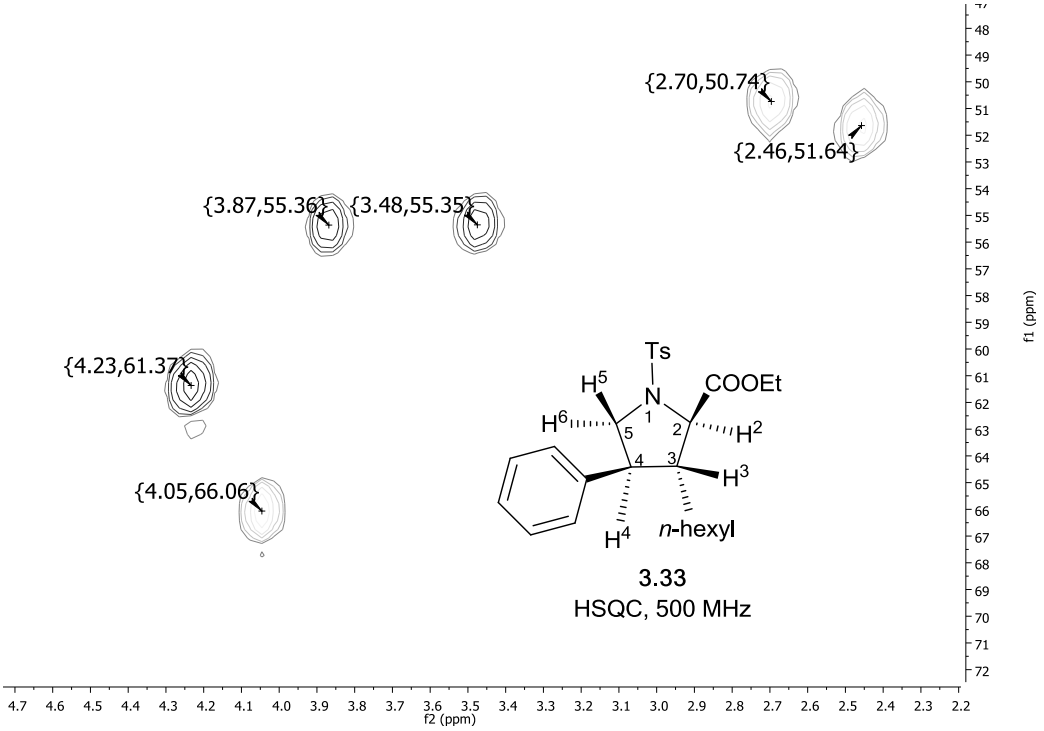
C_2 (84.14.0) - H^2 (5.30)

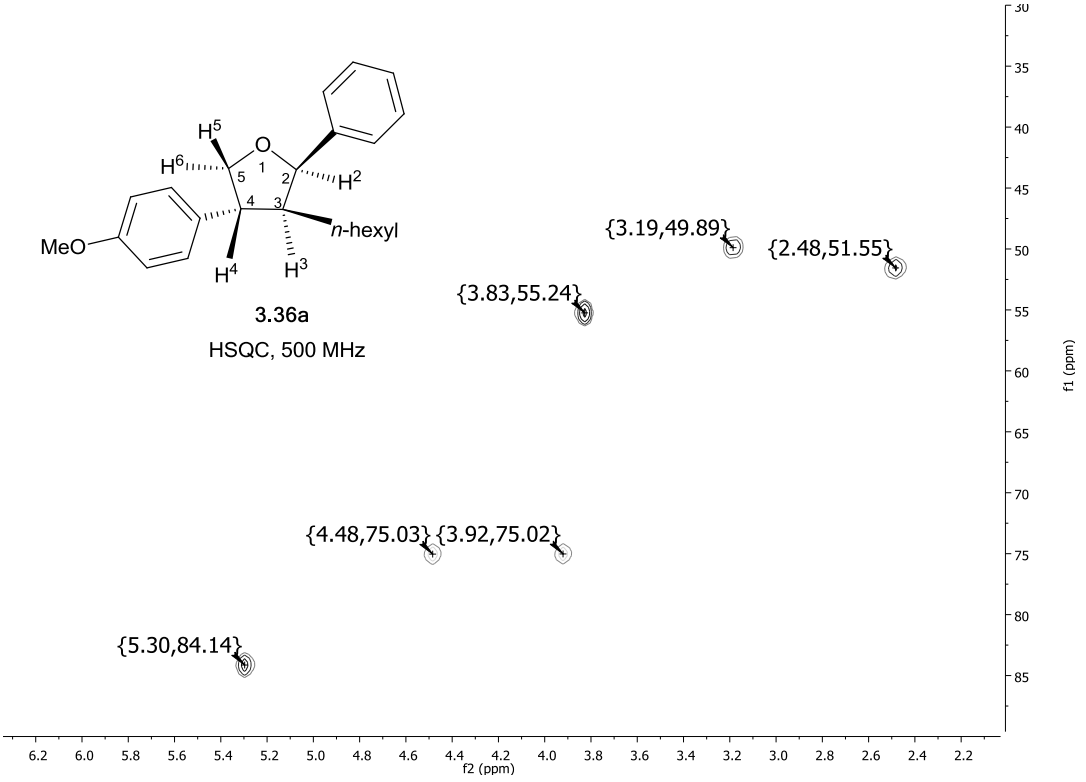
C_3 (51.5) - H^3 (2.48)

C_4 (49.9) - H^4 (3.19)

C_5 (75.0) - H^5 and H^6 (4.48 / 3.92)

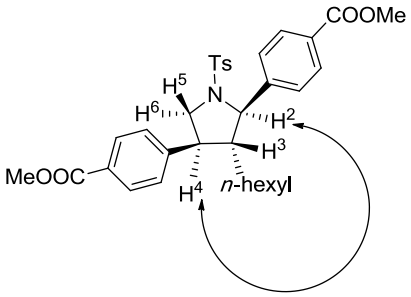



{2.70,50.74}
{2.46,51.64}
{3.87,55.36}
{3.48,55.35}
{4.23,61.37}
{4.05,66.06}
Ts
COOEt
H5
H6
H2
H3
H4
n-hexyl
1
2
3
4
5
N
3.33
HSQC, 500 MHz
f1 (ppm)
f2 (ppm)


H5
H6
H2
H3
H4
O
MeO
n-hexyl
1
2
3
4
5
3.36a
HSQC, 500 MHz
{3.19,49.89}
{2.48,51.55}
{3.83,55.24}
{4.48,75.03}
{3.92,75.02}
{5.30,84.14}
f1 (ppm)
f2 (ppm)

Assignment of relative stereochemistry of compounds 3.22, 3.33 and 3.36a using ^{1}H NMR NOE difference and HSQC ^{13}C - ^{1}H correlations

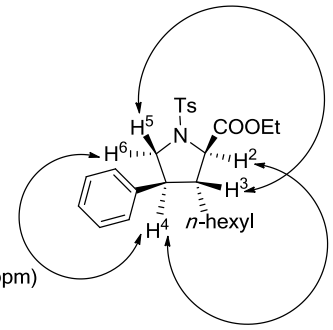
Irradiated (ppm)	Enhanced (ppm)	Significant correlation
4.43	7.99 7.41 2.83 2.35 1.31 0.86	H^2- H^4



H^2 (4.43 ppm) - H^4 (2.83 ppm)

Irradiated (ppm)	Enhanced (ppm)	Significant correlation
4.05	2.70	H^2- H^4
3.88	2.70	H^6- H^4
3.47	2.47	H^5- H^3

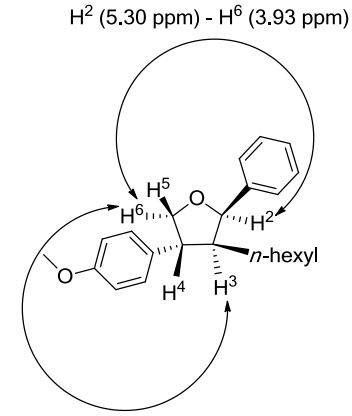
H^5 (3.47 ppm) - H^3 (2.47 ppm)



H^6 (3.88 ppm) - H^4 (2.70 ppm)

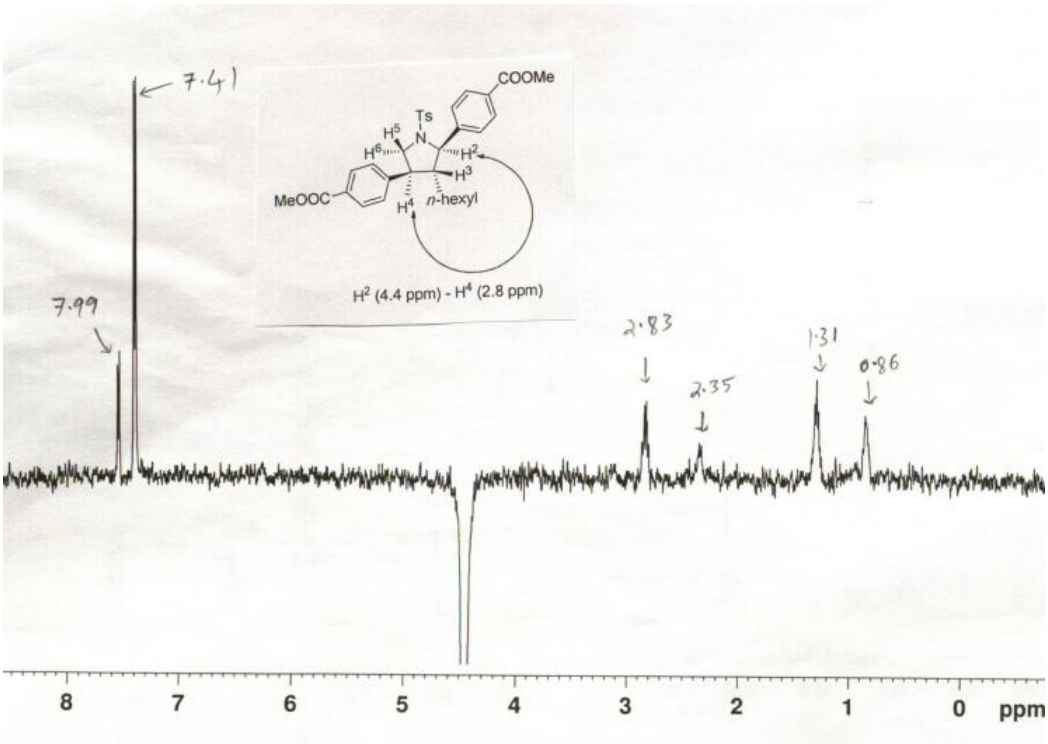
H^2 (4.05 ppm) - H^4 (2.70 ppm)

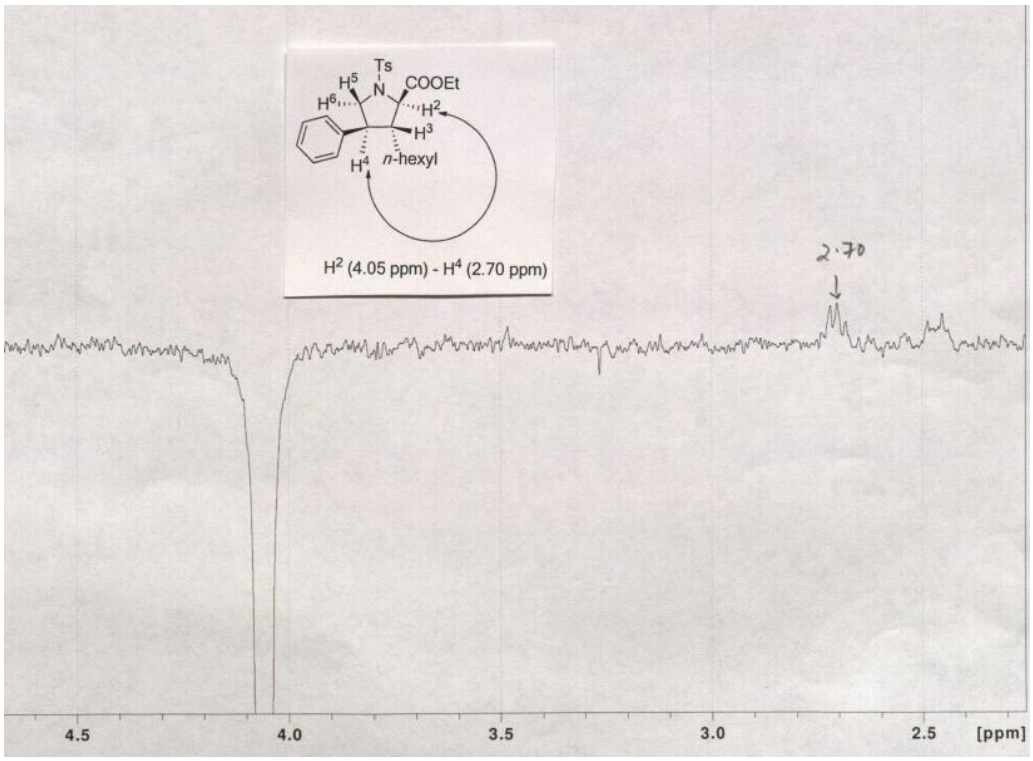
Irradiated (ppm)	Enhanced (ppm)	Significant correlation
5.30	7.30 3.93 2.49	H^2- H^3 H^2- H^6
3.19	7.31 7.23 4.50 3.92 2.47	H^4- H^5 Absence of H^4- H^2
2.48	7.24 5.30 3.92	H^3- H^2 H^3- H^6

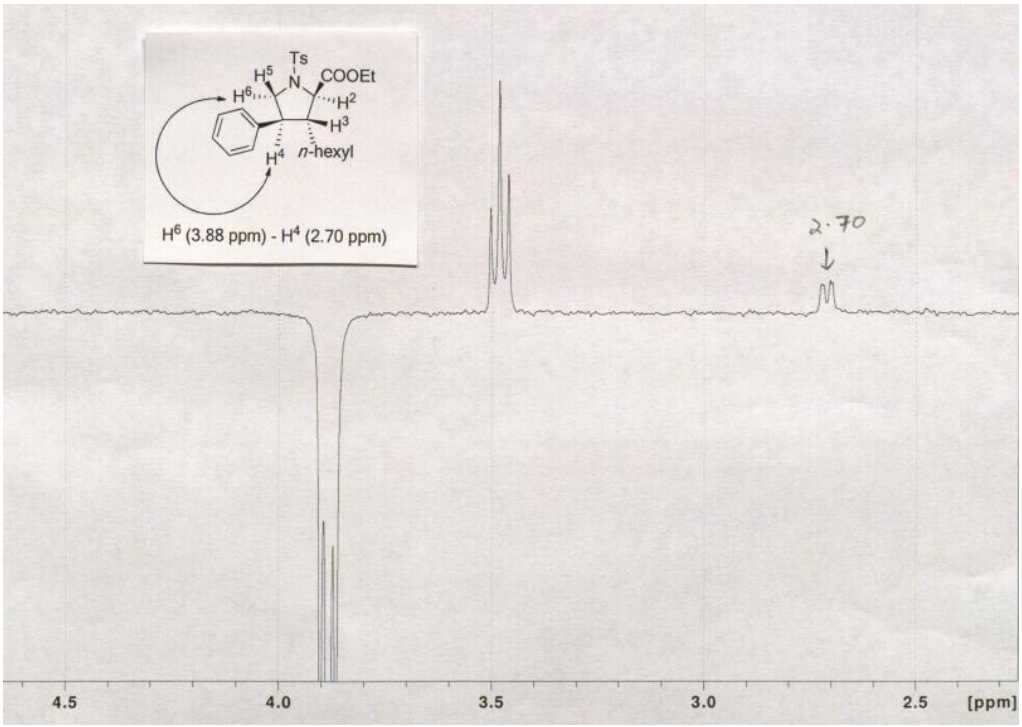


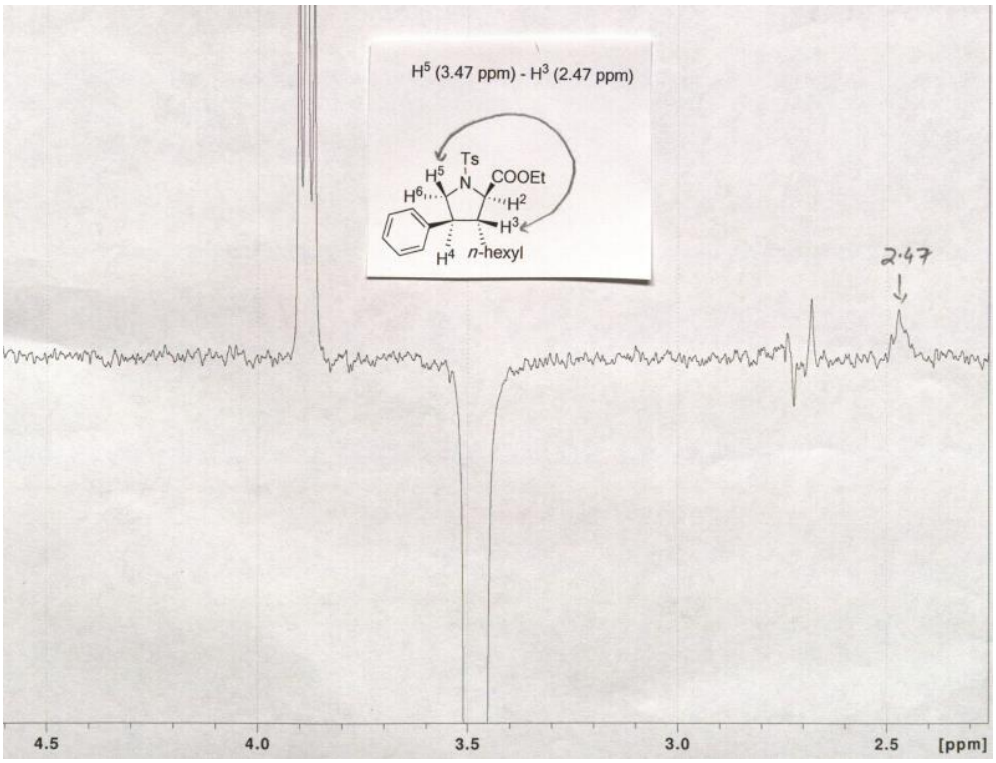
H^2 (5.30 ppm) - H^6 (3.93 ppm)

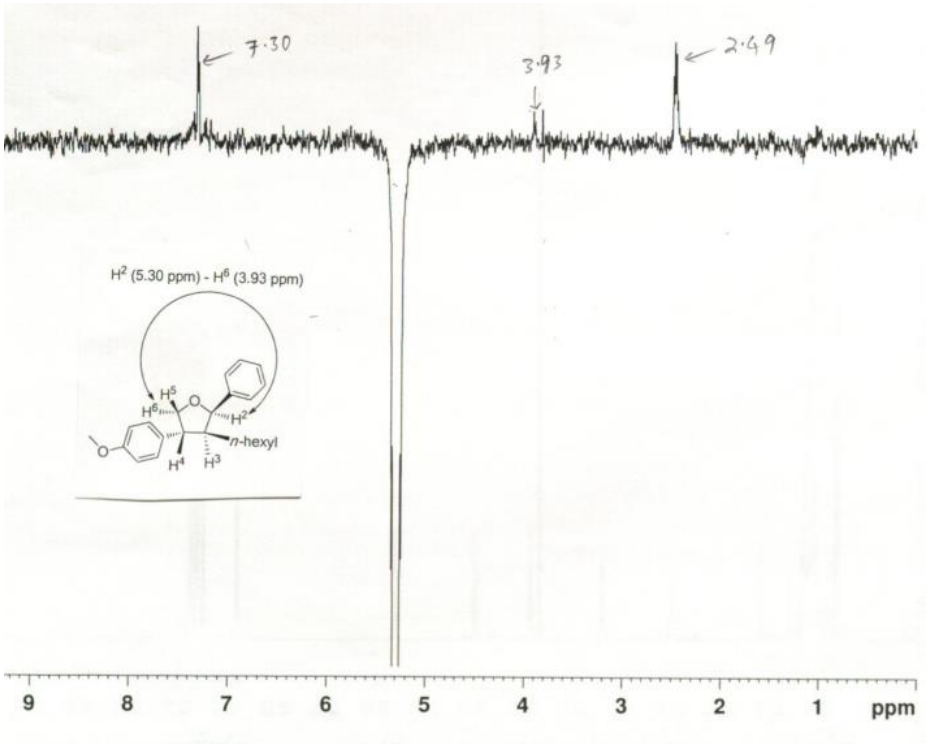
H^3 (2.48 ppm) - H^6 (3.92 ppm)

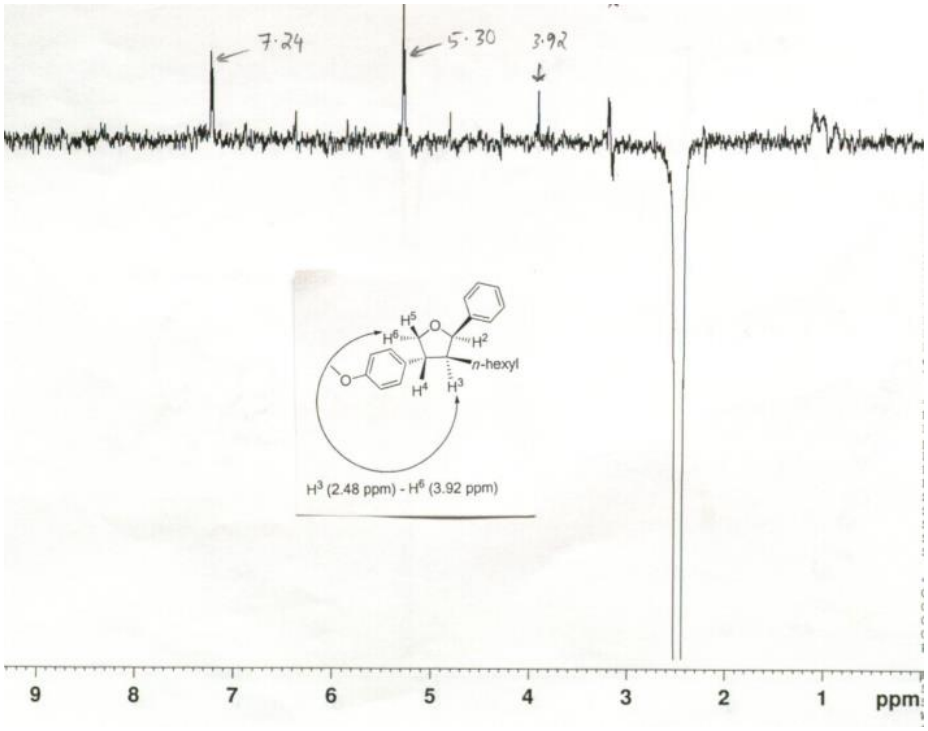


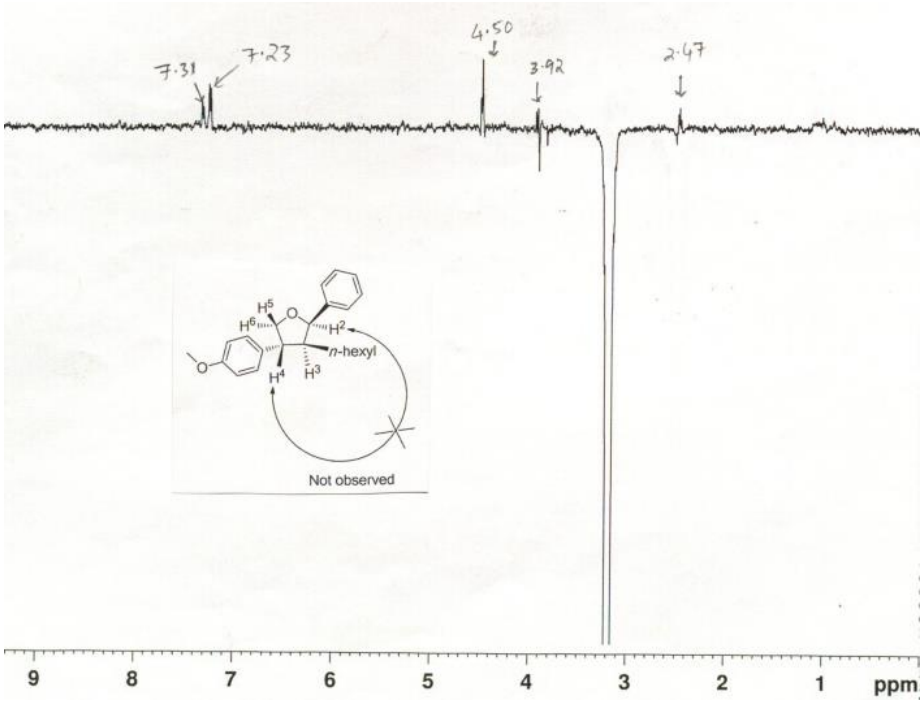

Ts
H5
N
COOEt
H6
H2
H3
H4
n-hexyl
H2 (4.05 ppm) - H4 (2.70 ppm)
2.70
4.5
4.0
3.5
3.0
2.5
[ppm]

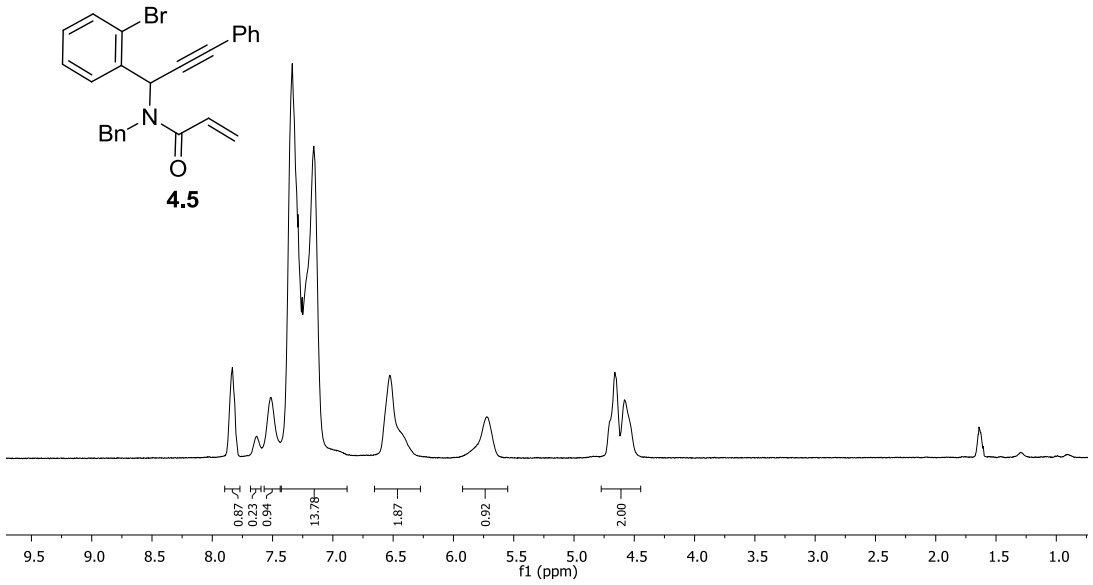

Ts
H5
N
COOEt
H6
H2
H3
H4
n-hexyl
H6 (3.88 ppm) - H4 (2.70 ppm)
2.70
4.5
4.0
3.5
3.0
2.5
[ppm]

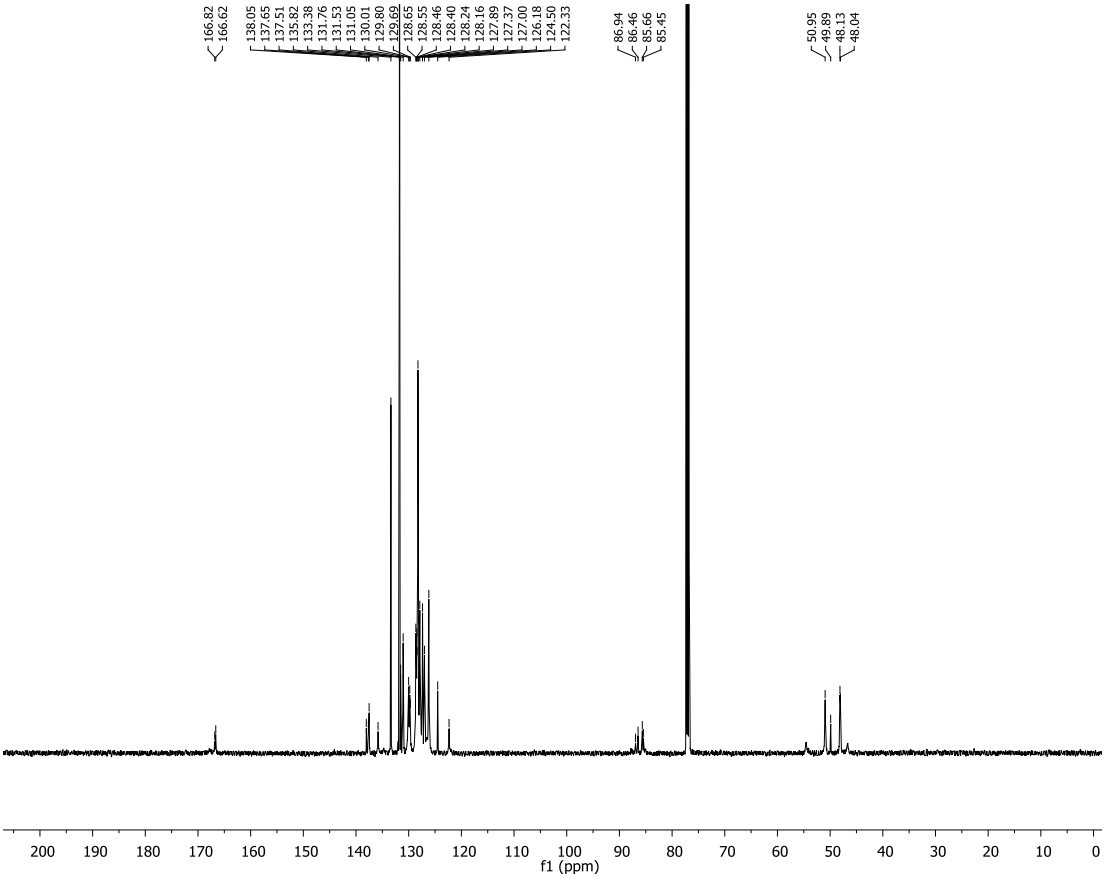

H5 (3.47 ppm) - H3 (2.47 ppm)
Ts
N
COOEt
H5
H6
H2
H3
H4
n-hexyl
2·47
4.5
4.0
3.5
3.0
2.5
[ppm]

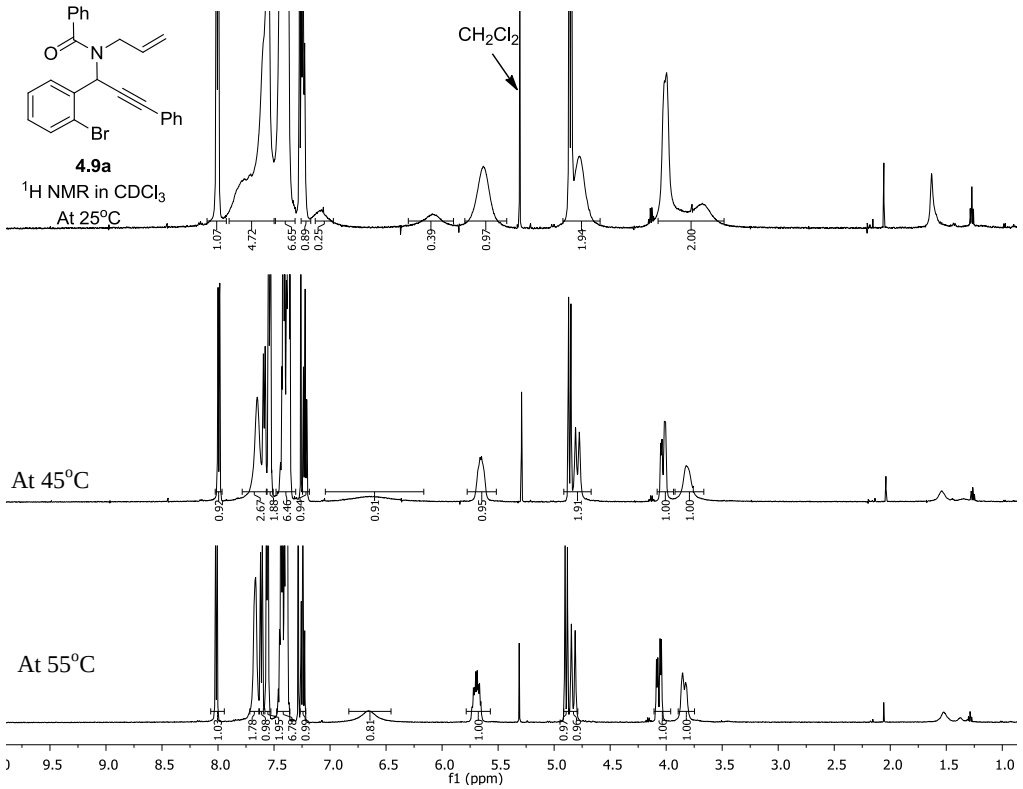

7·30
3·93
2·49
H2 (5.30 ppm) - H6 (3.93 ppm)
H5
H6
O
H2
n-hexyl
H4
H3
9
8
7
6
5
4
3
2
1
ppm

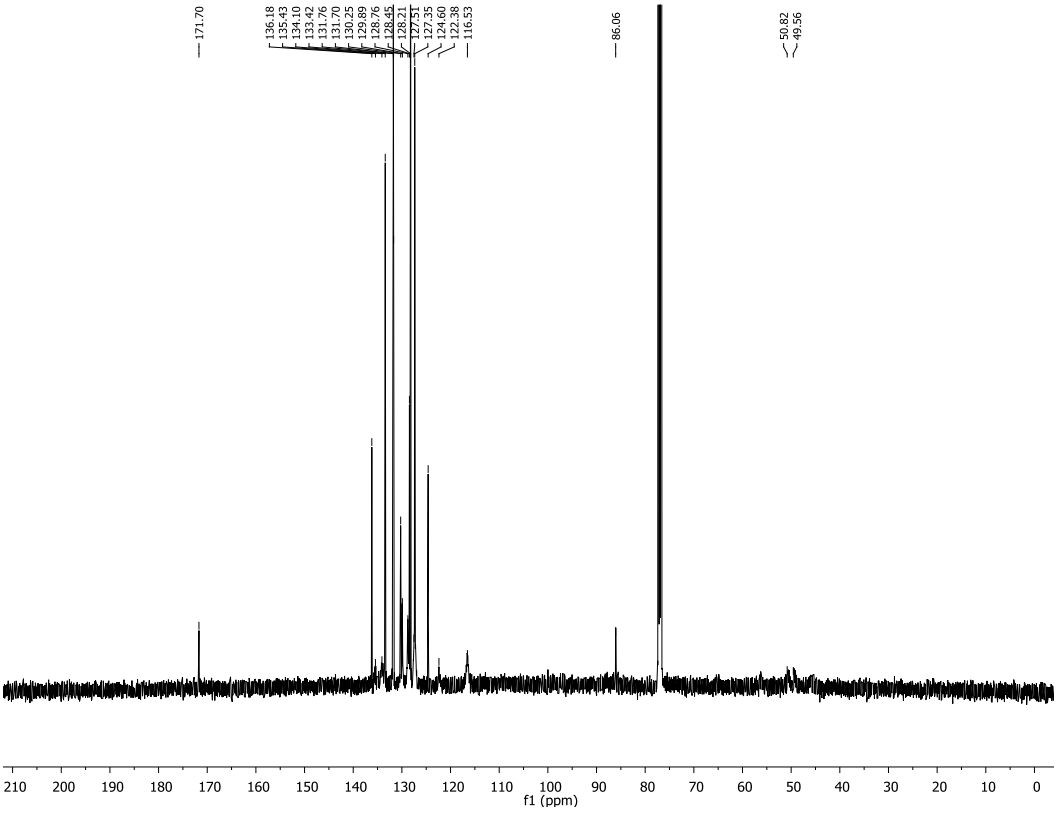

7·24
5·30
3·92
H5
H6
O
H2
n-hexyl
H4
H3
H3 (2.48 ppm) - H6 (3.92 ppm)
9
8
7
6
5
4
3
2
1
ppm

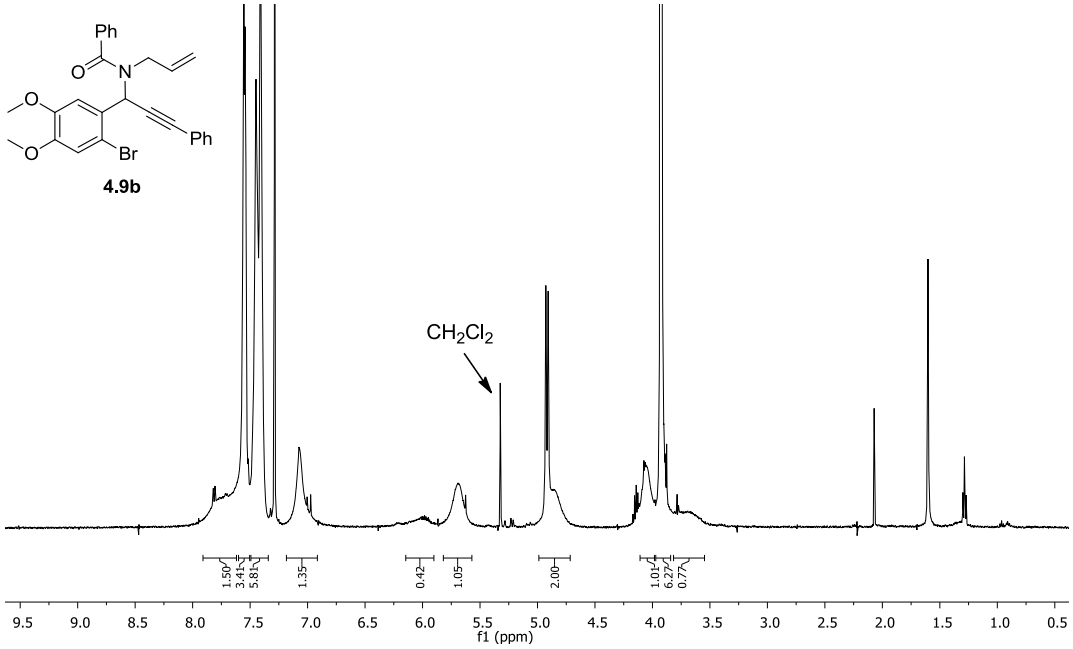

7·31
7·23
4·50
3·92
2·47
H5
H6
O
H2
n-hexyl
H4
H3
Not observed
9
8
7
6
5
4
3
2
1
ppm

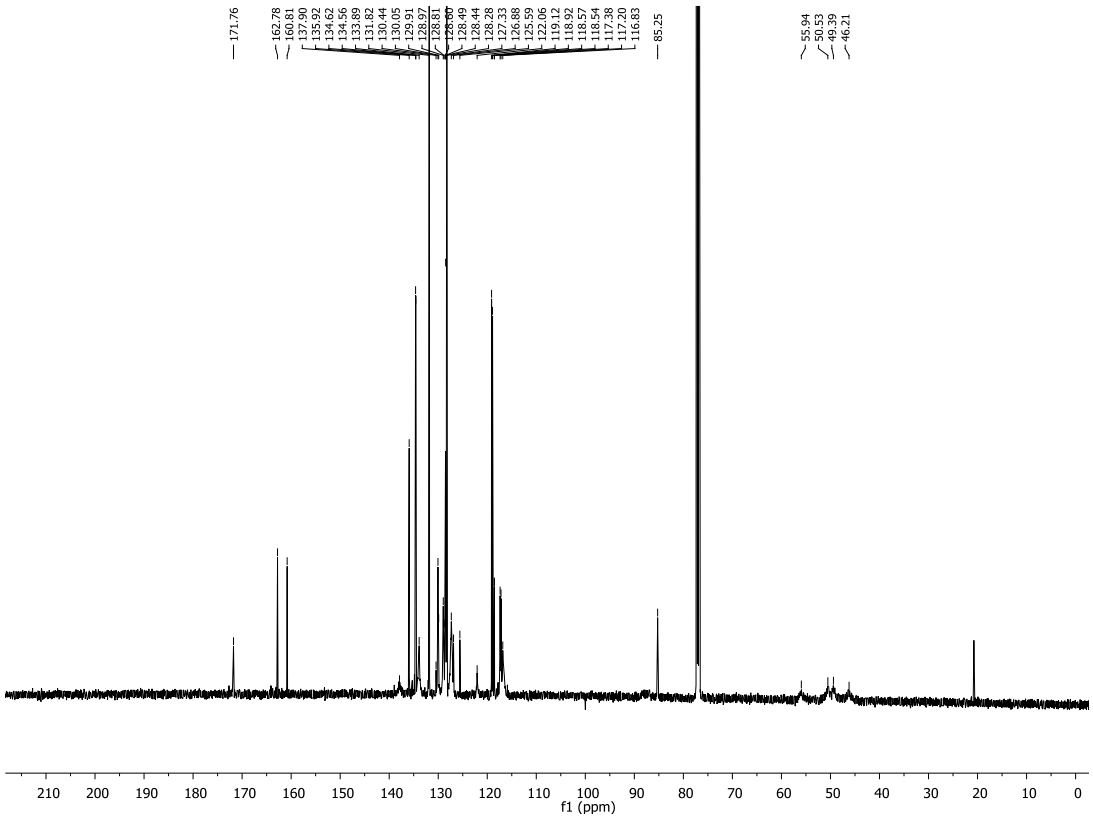

Br
Ph
N
Bn
O
4.5
0.87
0.23
0.94
13.78
1.87
0.92
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

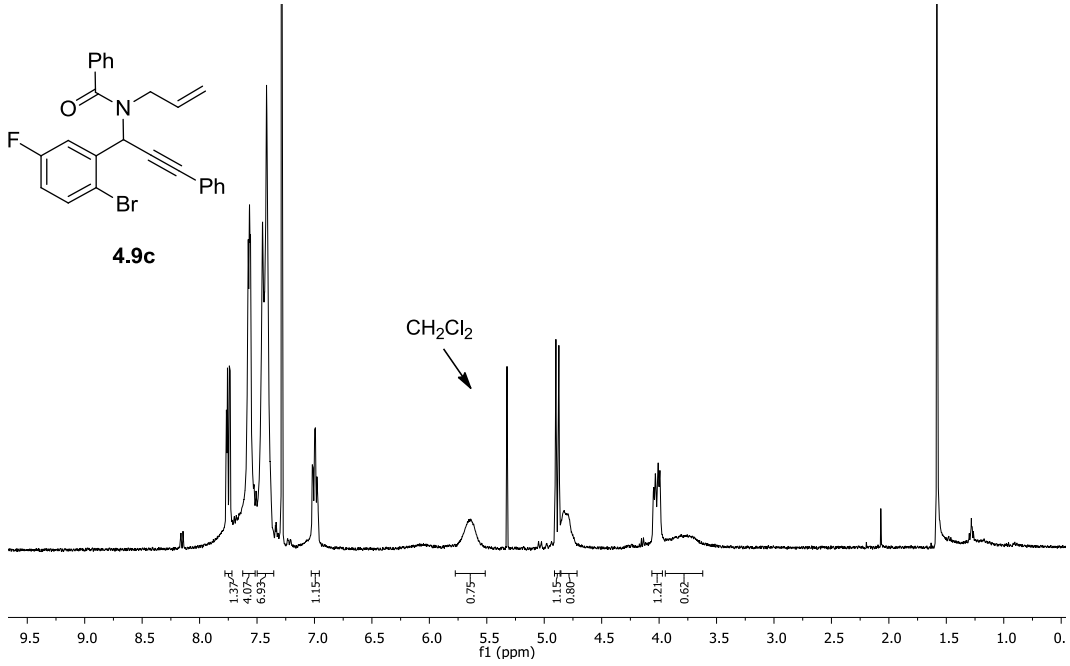

166.82
166.62
138.05
137.65
137.51
135.82
133.38
131.76
131.53
131.05
130.01
129.80
129.69
128.65
128.55
128.46
128.40
128.24
128.16
127.89
127.37
127.00
126.18
124.50
122.33
86.94
86.46
85.66
85.45
50.95
49.89
48.13
48.04
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

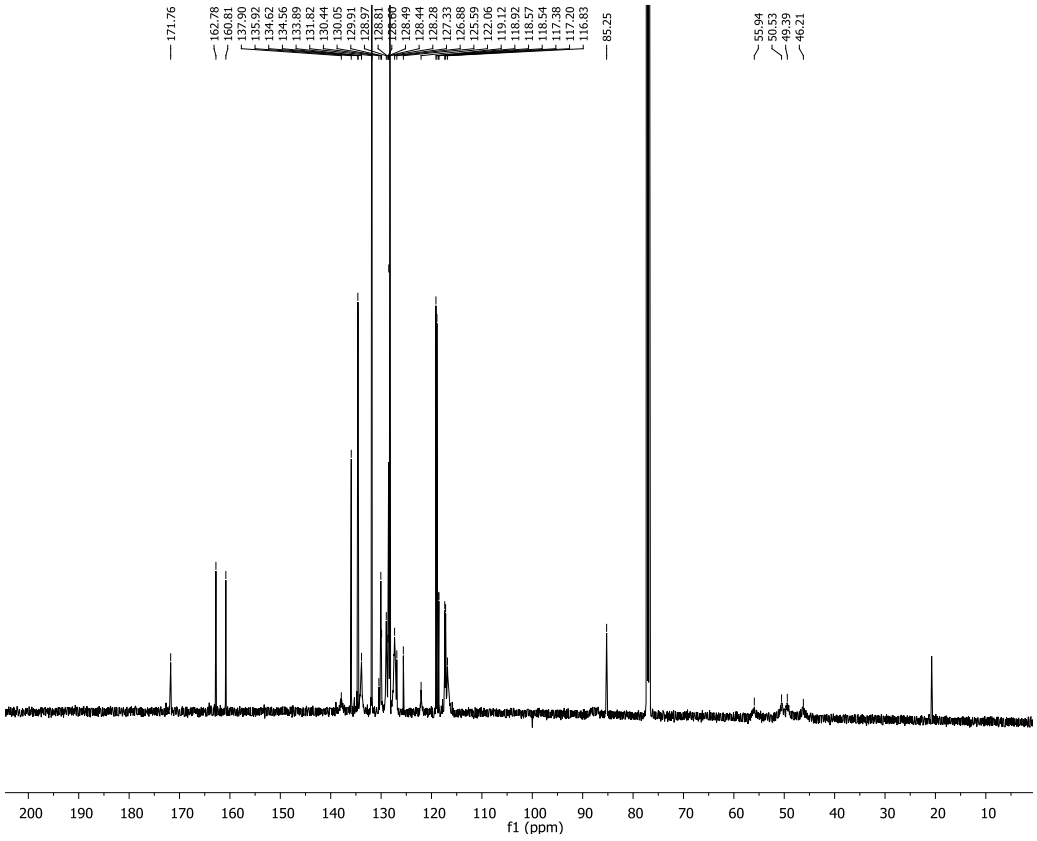

Ph
O
N
Ph
Br
4.9a
^{1}H NMR in $CDCl_3$
At 25°C
CH_2Cl_2
At 45°C
At 55°C
f1 (ppm)

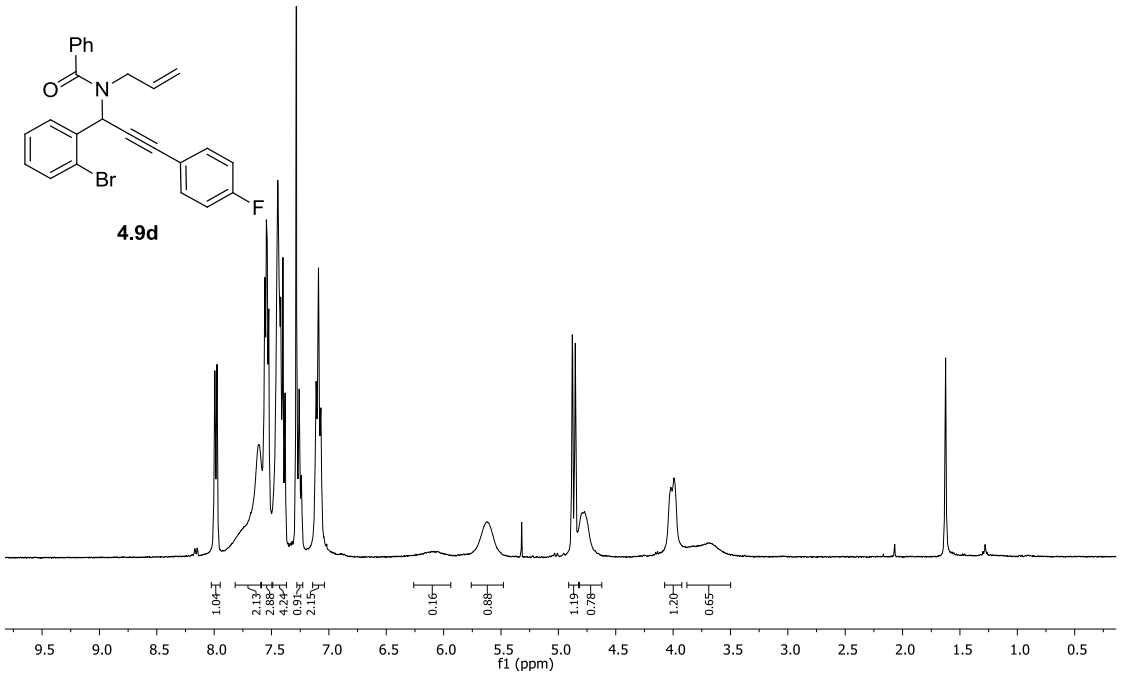

171.70
136.18
135.43
134.10
133.42
131.76
131.70
130.25
129.89
128.76
128.45
128.21
127.51
127.35
124.60
122.38
116.53
86.06
50.82
49.56
f1 (ppm)

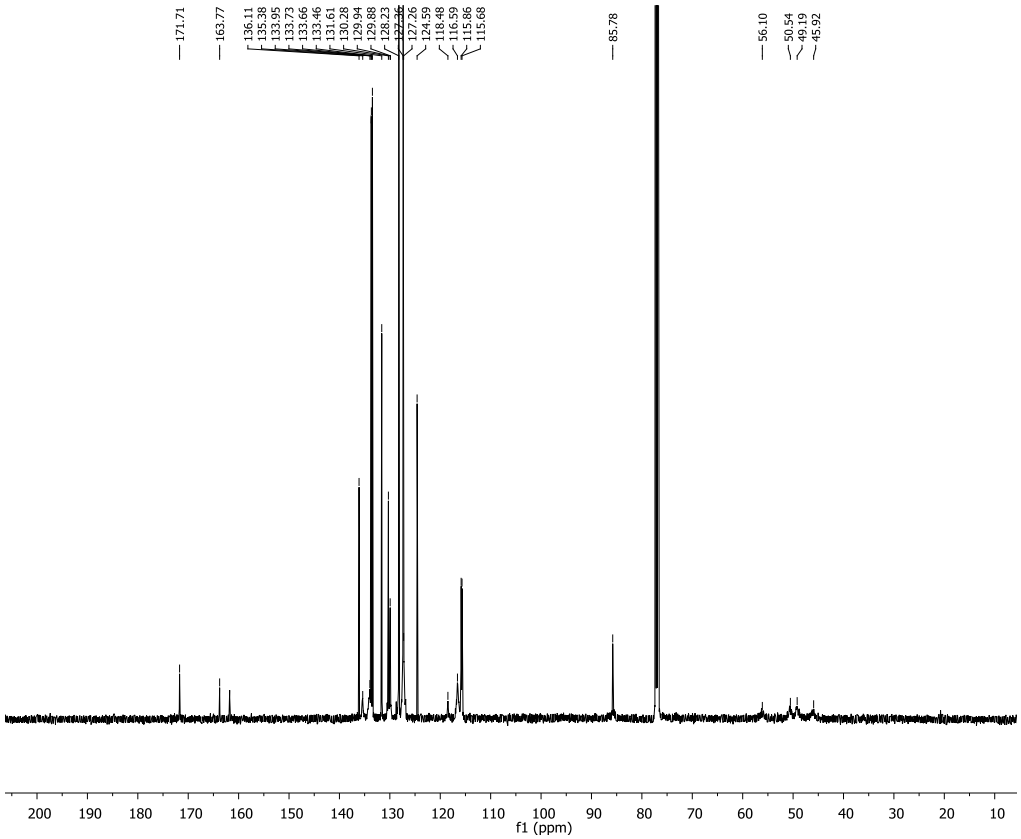

Ph
O
N
O
O
Br
Ph
4.9b
CH2Cl2
1.50
3.41
5.81
1.35
0.42
1.05
2.00
1.01
6.27
0.77
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

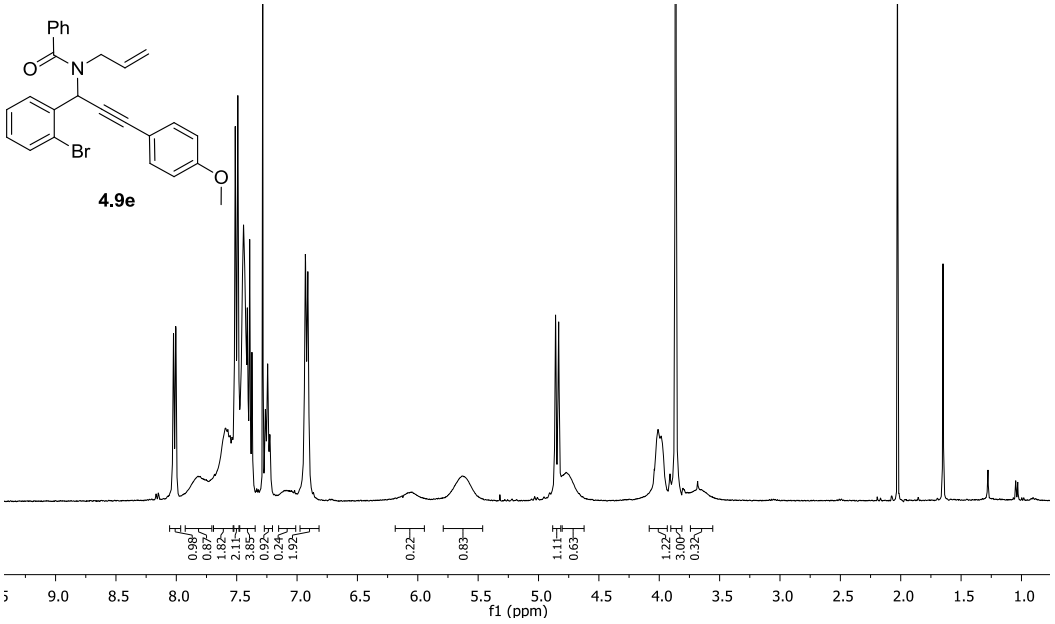

171.76
162.78
160.81
137.90
135.92
134.62
134.56
133.89
131.82
130.44
130.05
129.91
128.97
128.81
128.60
128.49
128.44
128.28
127.33
126.88
125.99
122.96
119.12
118.92
118.57
118.54
117.38
117.20
116.83
85.25
55.94
50.53
49.39
46.21
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

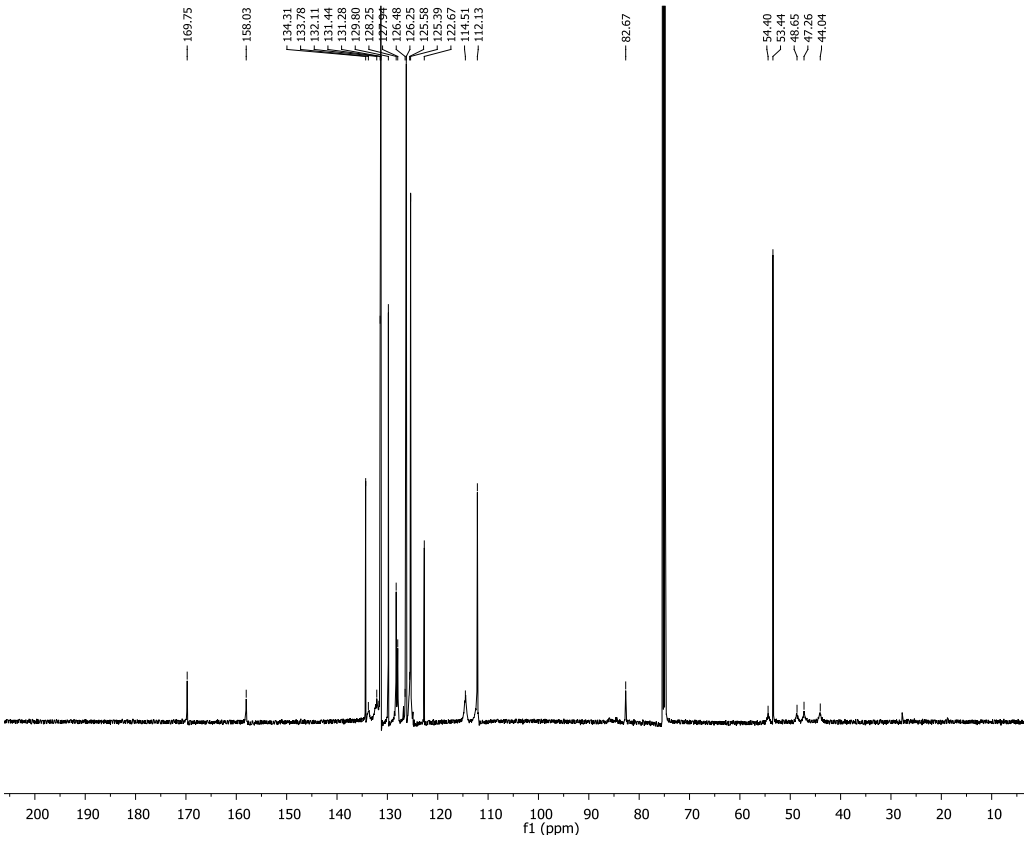

Ph
O
N
F
Br
Ph
4.9c
CH2Cl2
1.37
4.07
6.93
1.15
0.75
1.15
0.80
1.21
0.62
f1 (ppm)

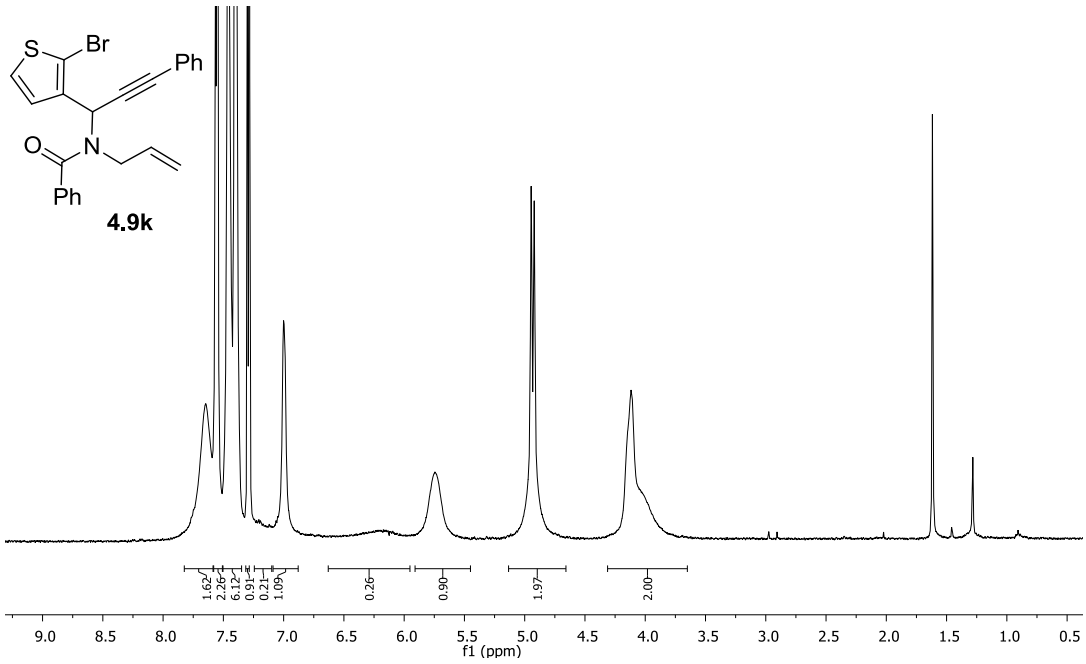

171.76
162.78
160.81
137.90
135.92
134.62
134.56
133.89
131.82
130.44
130.05
129.91
128.87
128.49
128.44
128.28
127.33
126.88
125.59
122.06
119.12
118.92
118.57
118.54
117.38
117.20
116.83
85.25
55.94
50.53
49.39
46.21
f1 (ppm)

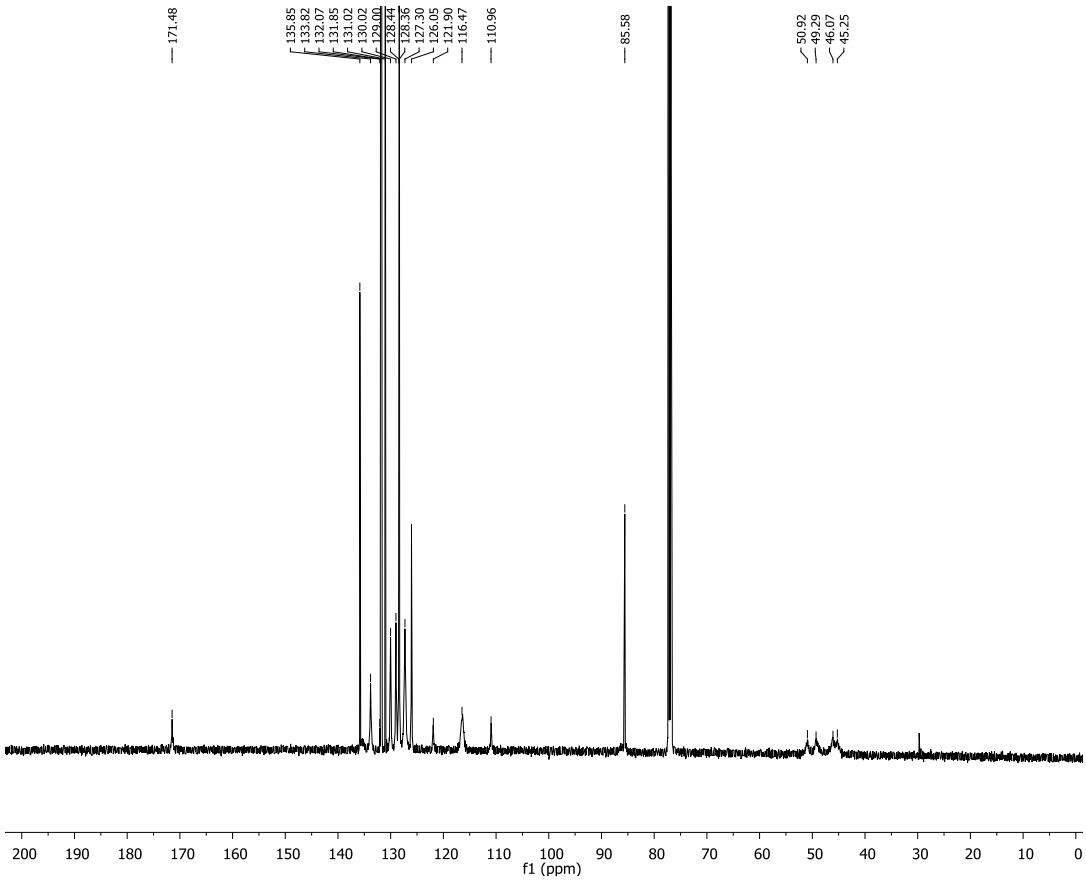

Ph
O
N
Br
F
4.9d
1.04
2.13
2.88
4.24
0.91
2.15
0.16
0.88
1.19
0.78
1.20
0.65
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

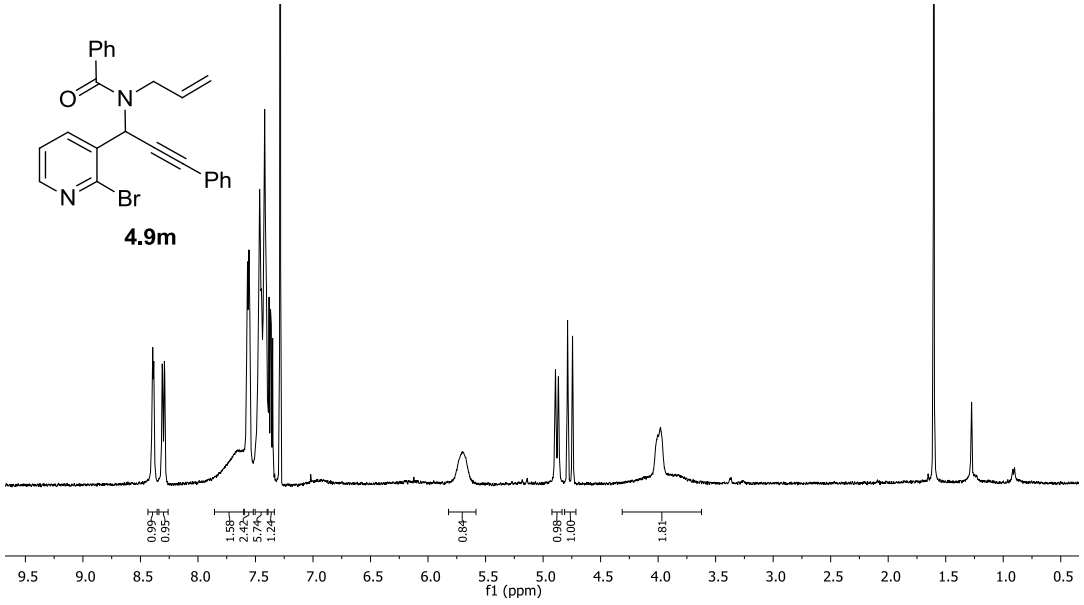

171.71
163.77
136.11
135.38
133.95
133.73
133.66
133.46
131.61
130.28
129.94
129.88
128.23
127.36
124.59
118.48
116.59
115.86
115.68
85.78
56.10
50.54
49.19
45.92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

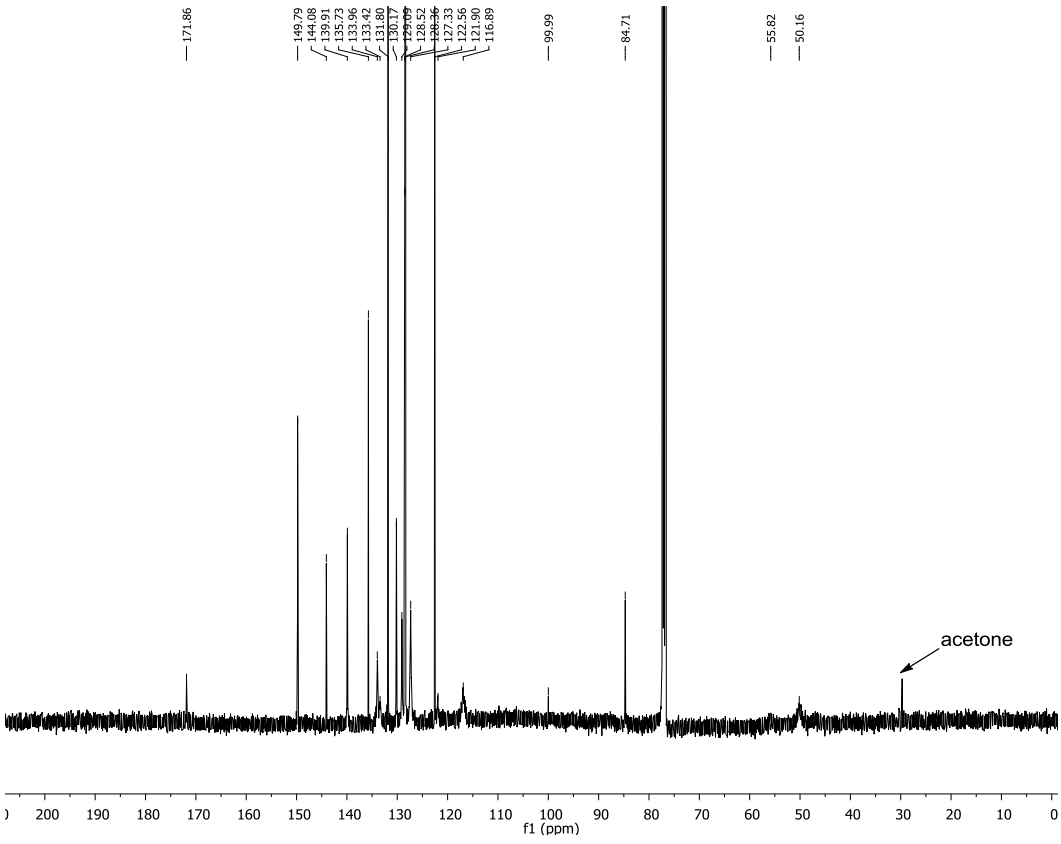

Ph
O
N
Br
O
4.9e
0.99
0.87
1.82
2.11
3.85
0.92
0.24
1.92
0.22
0.83
1.11
0.63
1.22
3.00
0.32
f1 (ppm)

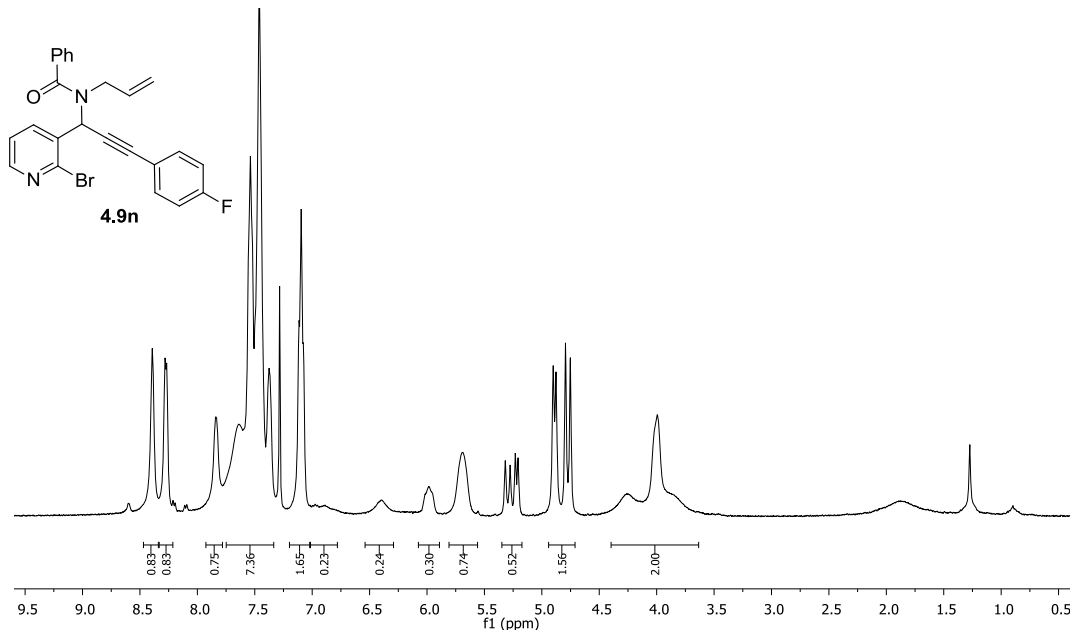

169.75
158.03
134.31
133.78
132.11
131.44
131.28
129.80
128.25
127.97
126.48
126.25
125.58
125.39
122.67
114.51
112.13
82.67
54.40
53.44
48.65
47.26
44.04
f1 (ppm)

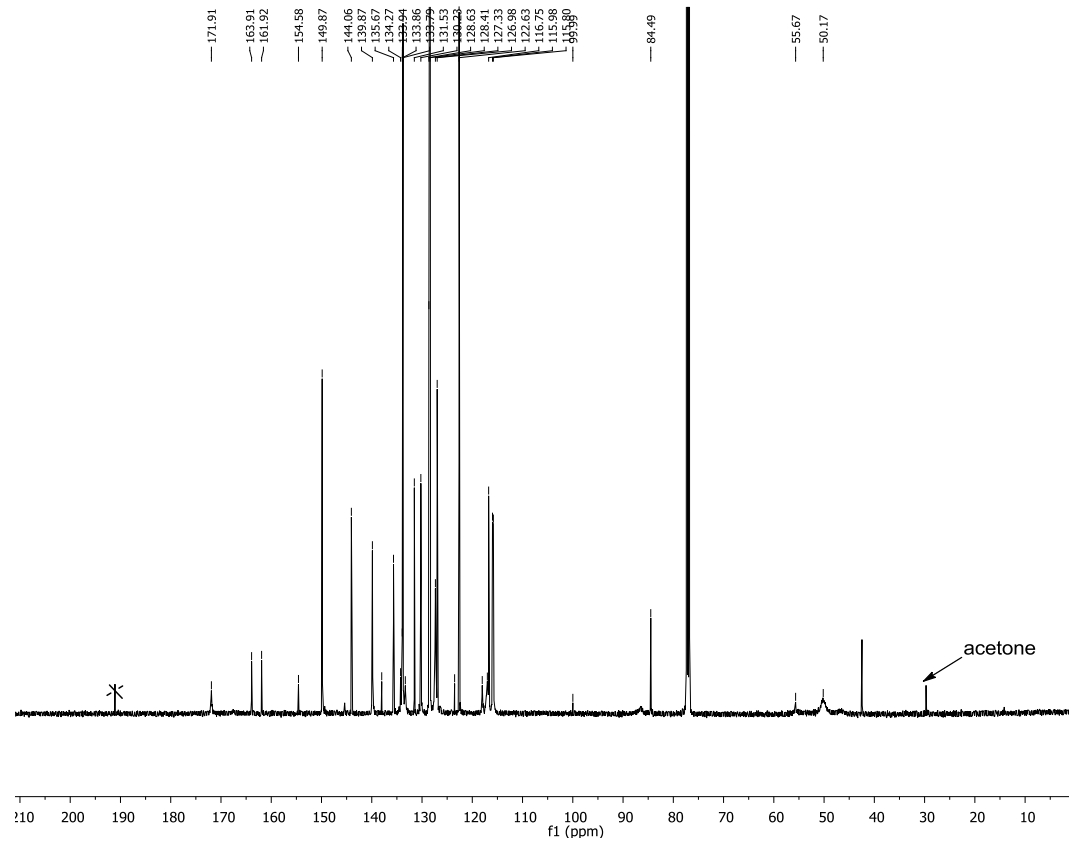

S
Br
Ph
O
N
Ph
4.9k
1.62
2.26
6.12
0.91
0.21
1.09
0.26
0.90
1.97
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

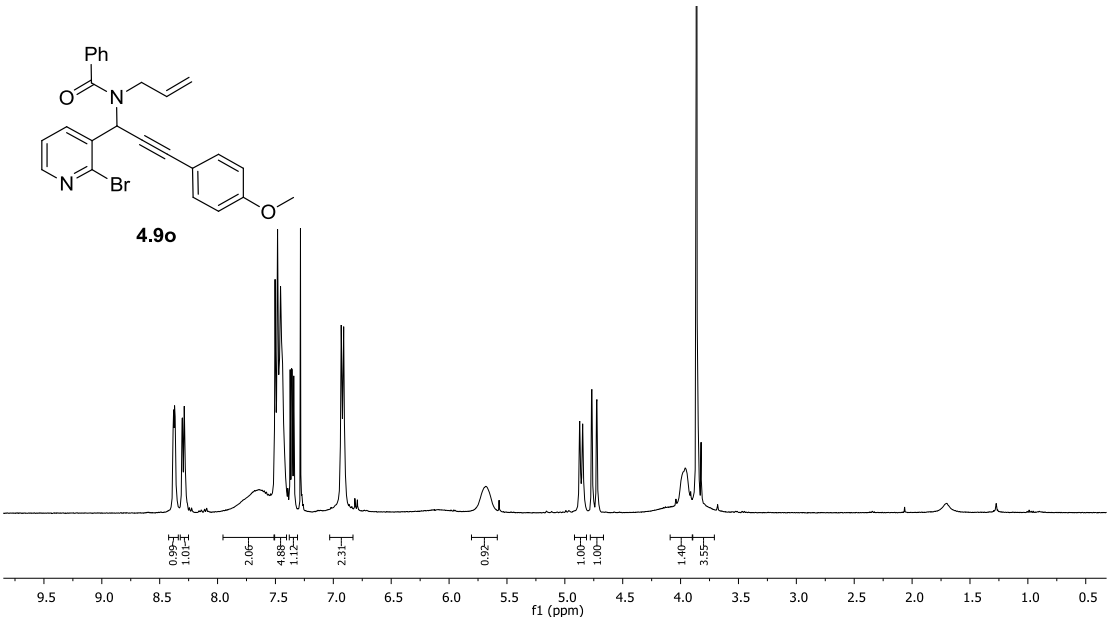

171.48
135.85
133.82
132.07
131.85
131.02
130.02
129.00
128.44
128.36
127.30
126.05
121.90
116.47
110.96
85.58
50.92
49.29
46.07
45.25
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

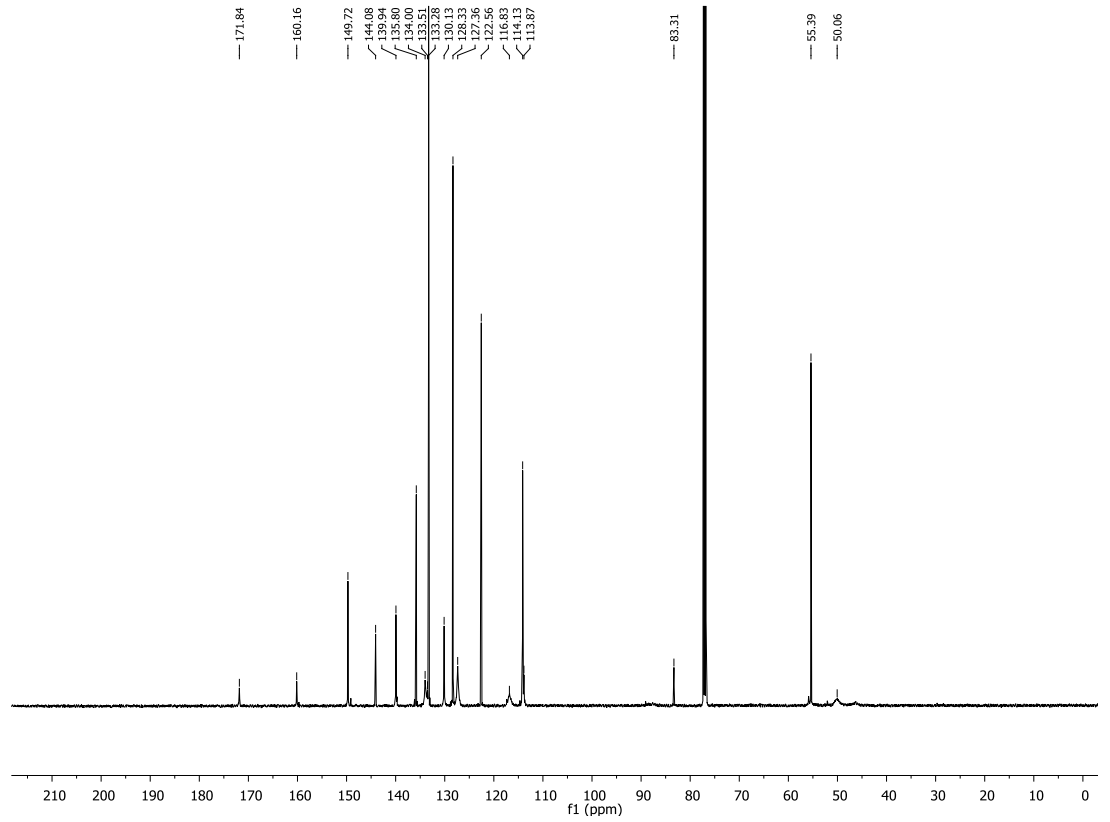

Ph
O
N
Ph
N
Br
4.9m
0.99
0.95
1.58
2.42
5.74
1.24
0.84
0.98
1.00
1.81
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

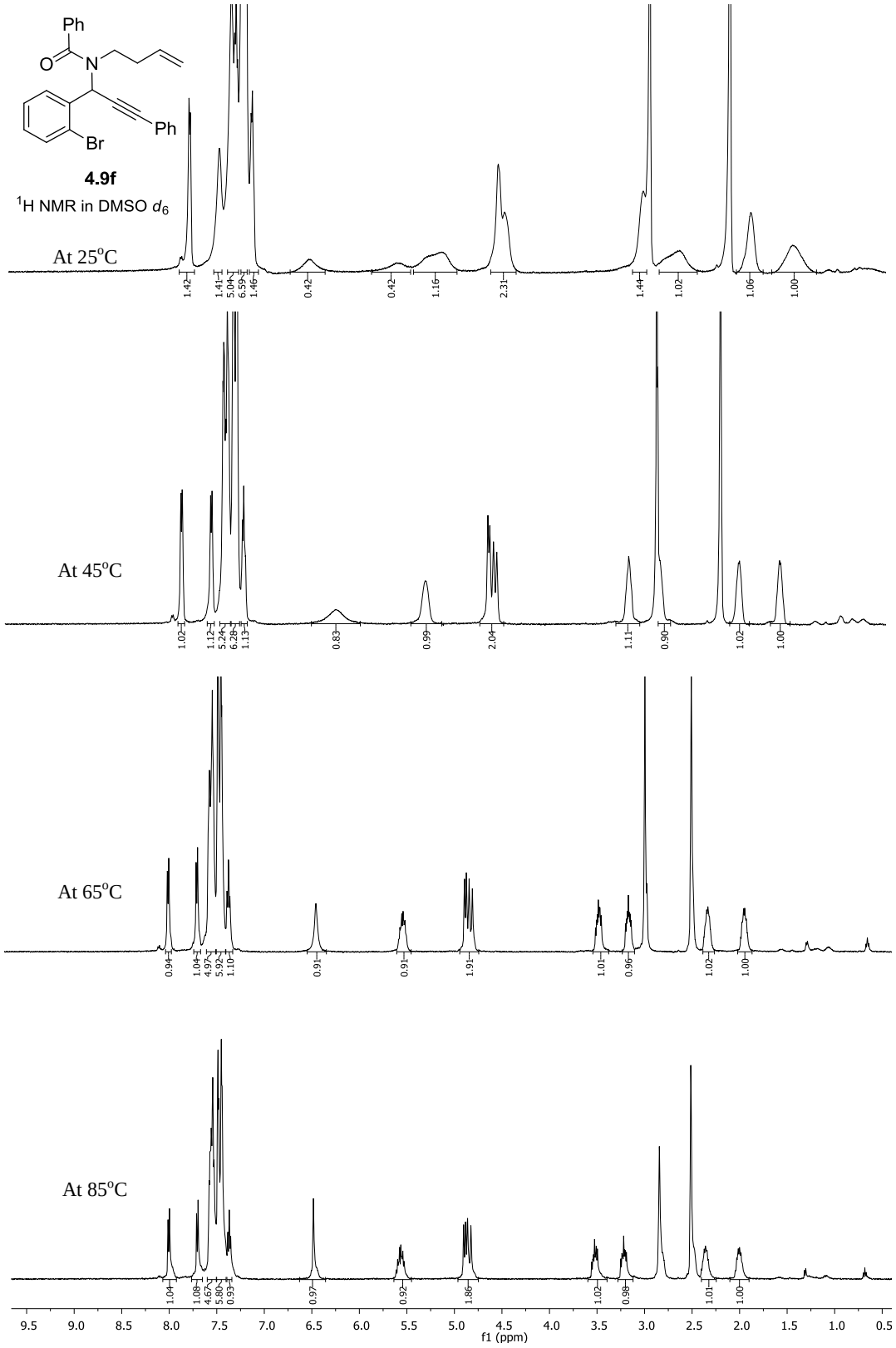

171.86
149.79
144.08
139.91
135.73
133.96
133.42
131.80
130.17
129.09
128.52
128.36
127.33
122.55
121.90
116.89
99.99
84.71
55.82
50.16
acetone
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

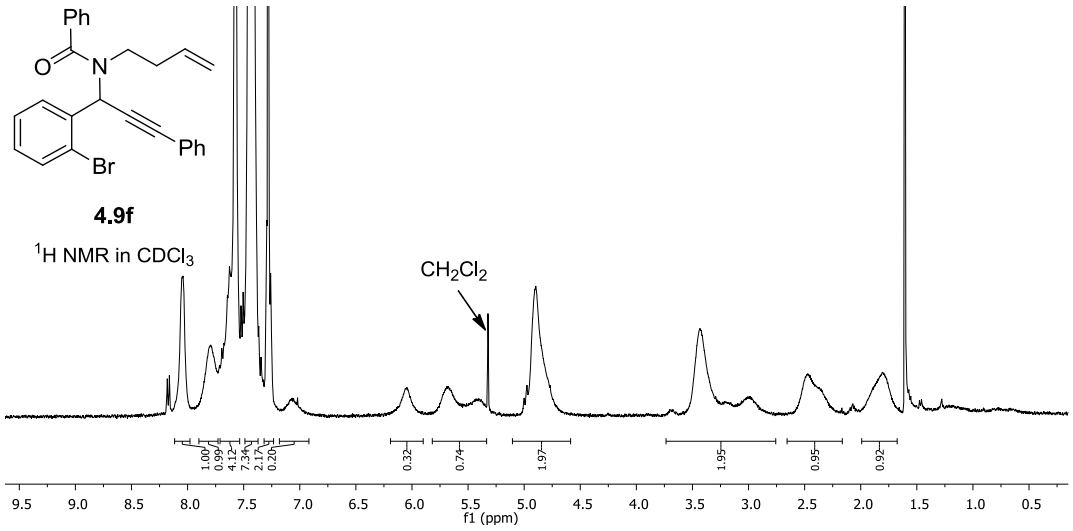

Ph
O
N
N
Br
F
4.9n
0.83
0.83
0.75
7.36
1.65
0.23
0.24
0.30
0.74
0.52
1.56
2.00
f1 (ppm)

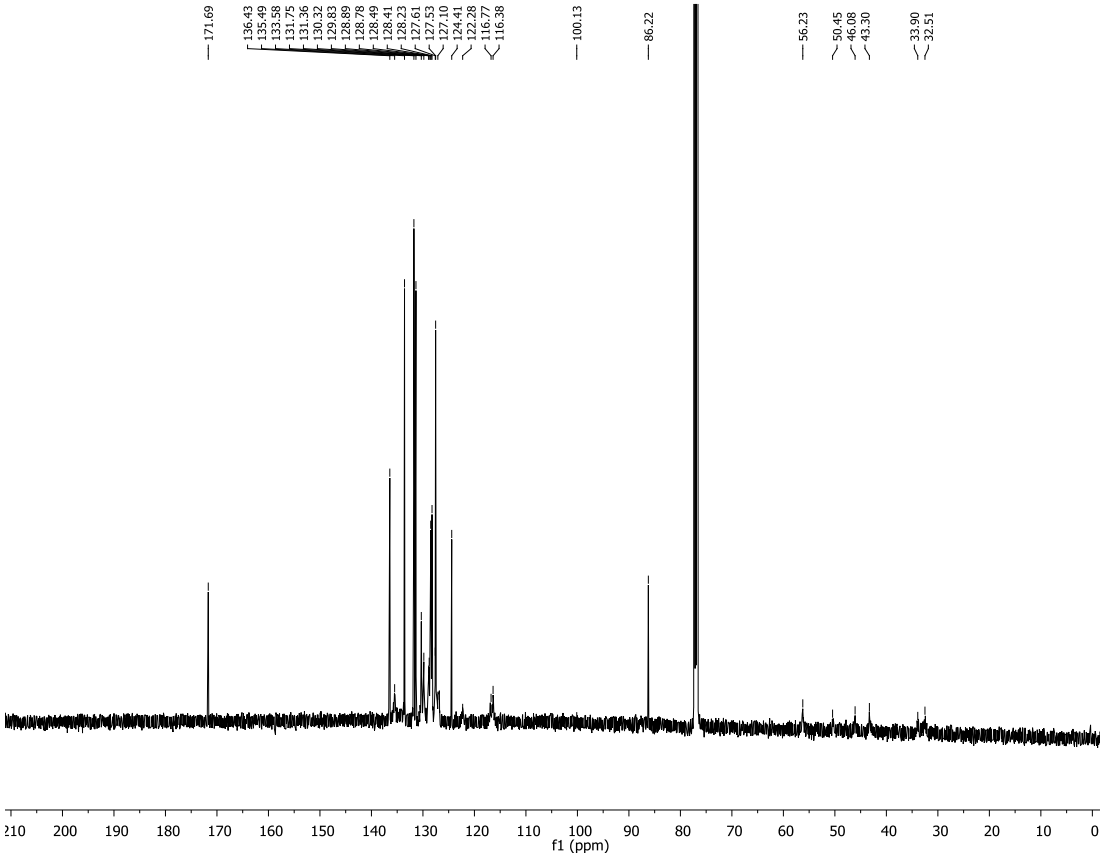

171.91
163.91
161.92
154.58
149.87
144.06
139.87
135.67
134.27
84.49
55.67
50.17
acetone
f1 (ppm)

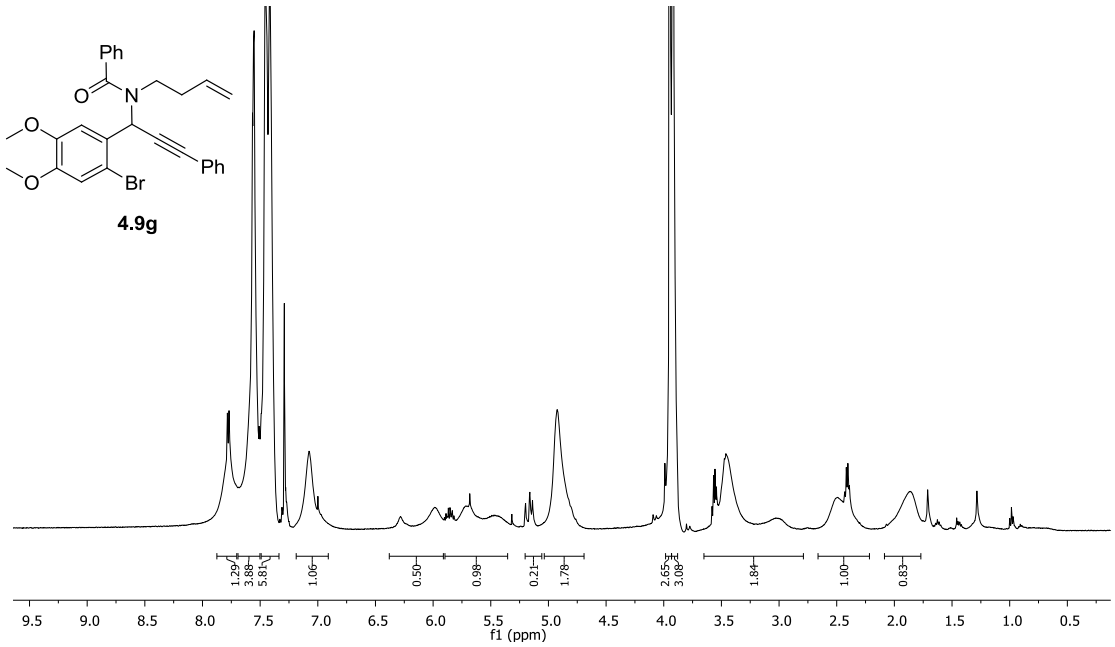

Ph
O
N
N
Br
O
4.9o
0.99
1.01
2.06
4.88
1.12
2.31
0.92
1.00
1.00
1.40
3.55
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

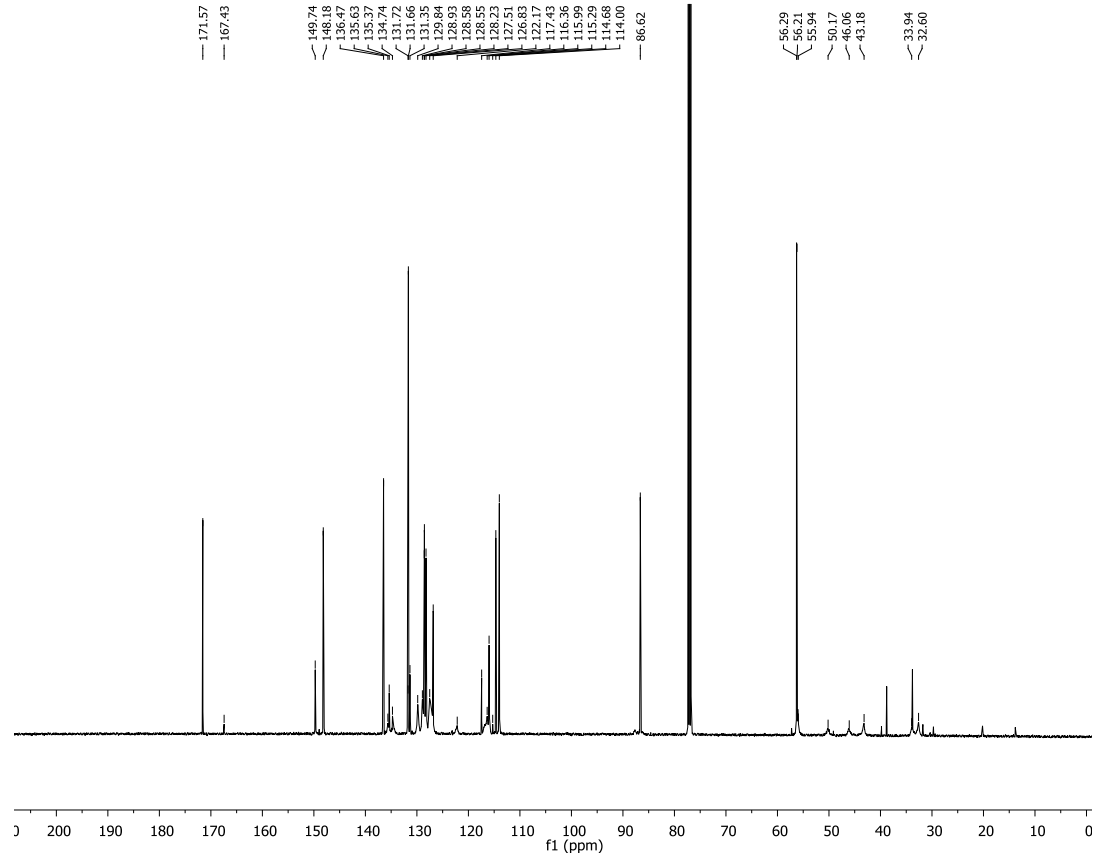

171.84
160.16
149.72
144.08
139.94
135.80
134.00
133.51
133.28
130.13
128.33
127.36
122.56
116.83
114.13
113.87
83.31
55.39
50.06
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

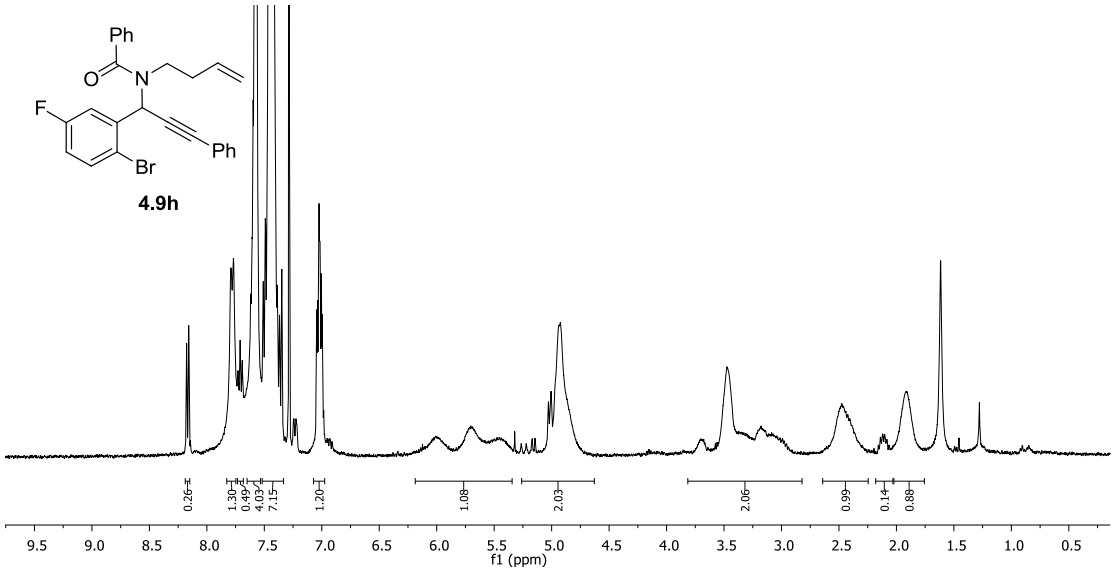

Ph
O
N
Ph
Br
4.9f
1H NMR in DMSO d6
At 25°C
At 45°C
At 65°C
At 85°C
f1 (ppm)

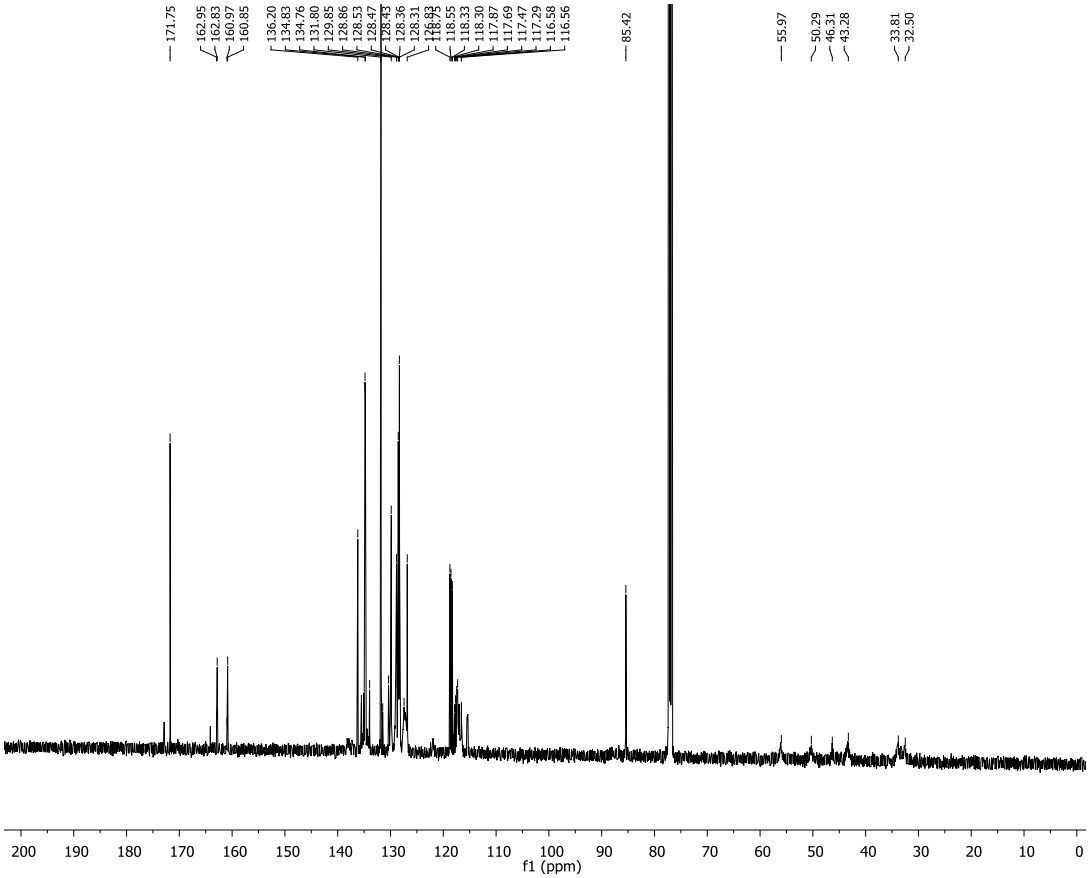

Ph
O
N
Ph
Br
4.9f
^{1}H NMR in $CDCl_3$
CH_2Cl_2
1.00
0.99
4.12
7.34
2.17
0.20
0.32
0.74
1.97
1.95
0.95
0.92
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

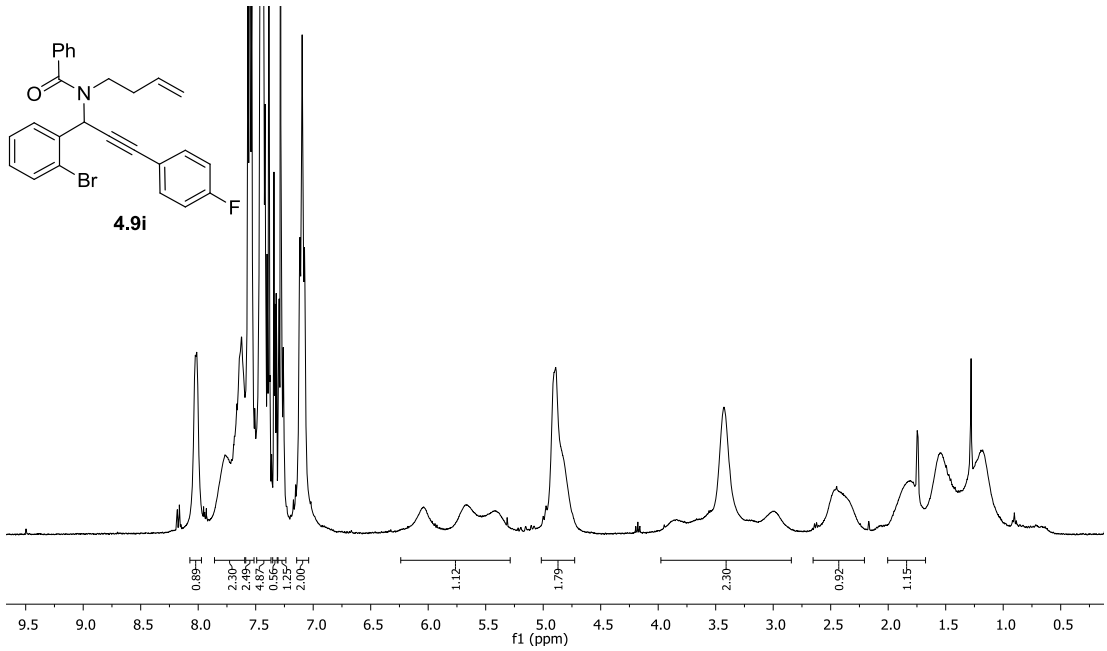

171.69
136.43
135.49
133.58
131.75
131.36
130.32
129.83
128.89
128.78
128.49
128.41
128.23
127.61
127.53
127.10
124.41
122.28
116.77
116.38
100.13
86.22
56.23
50.45
46.08
43.30
33.90
32.51
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

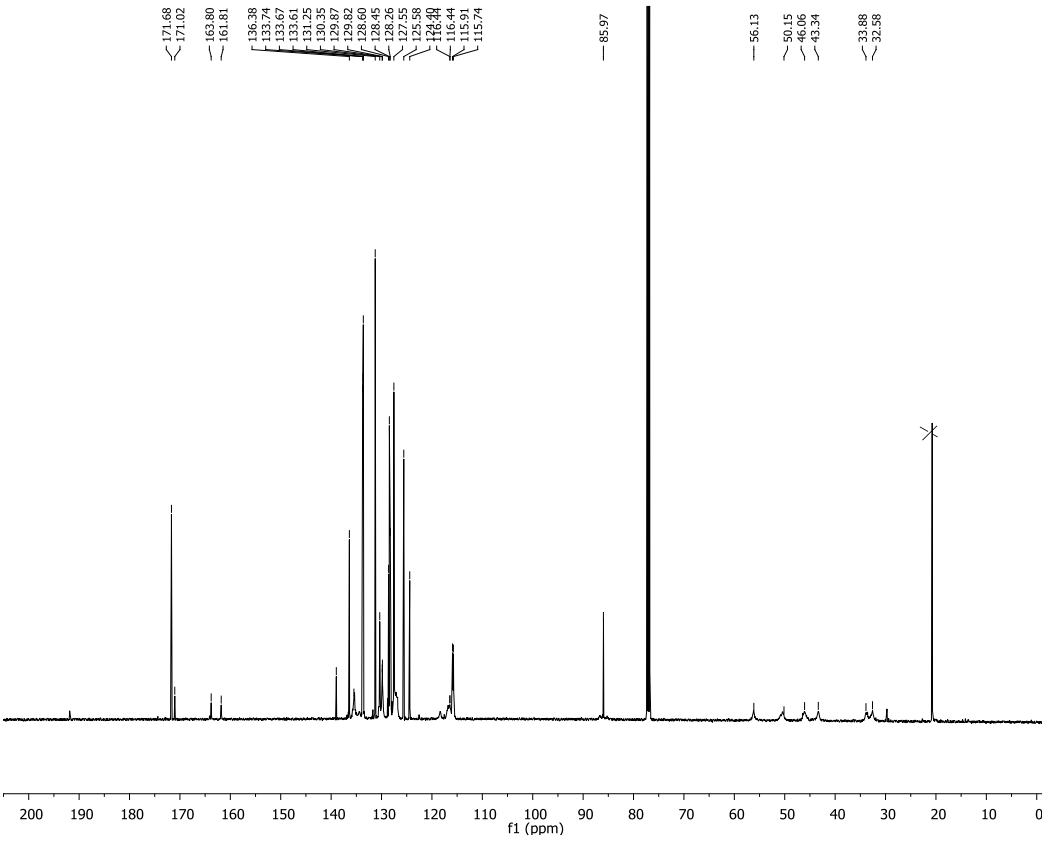

Ph
O
N
O
O
Br
Ph
4.9g
1.29
3.88
5.81
1.06
0.50
0.98
0.21
1.78
2.65
3.08
1.84
1.00
0.83
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

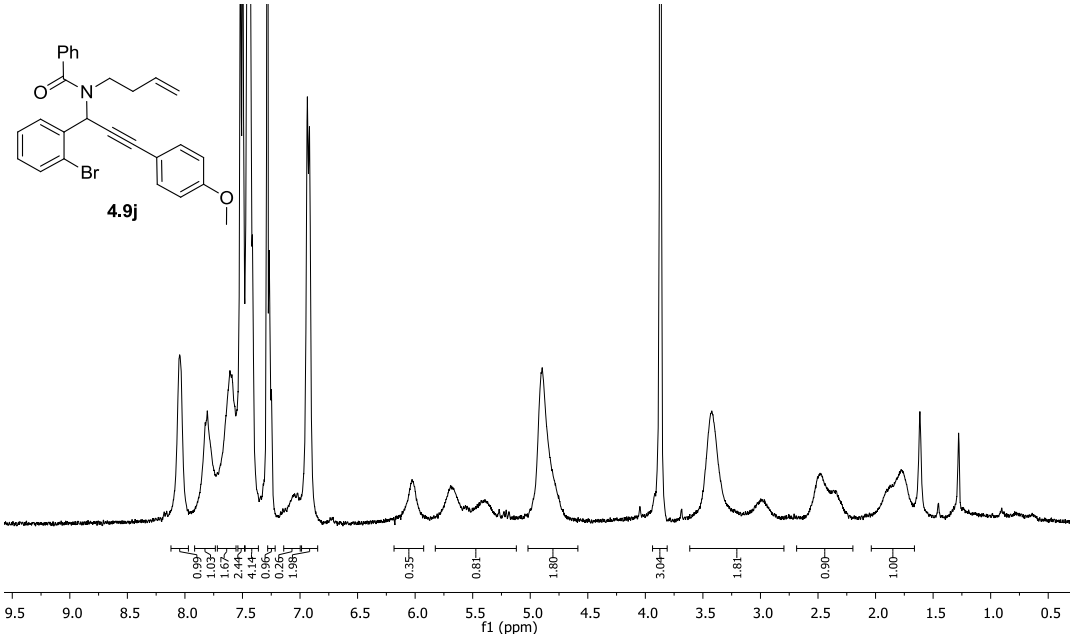

171.57
167.43
149.74
148.18
136.47
135.63
135.37
134.74
131.72
131.66
131.35
129.84
128.93
128.58
128.55
128.23
127.51
126.83
122.17
117.43
116.36
115.99
115.29
114.68
114.00
86.62
56.29
56.21
55.94
50.17
46.06
43.18
33.94
32.60
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

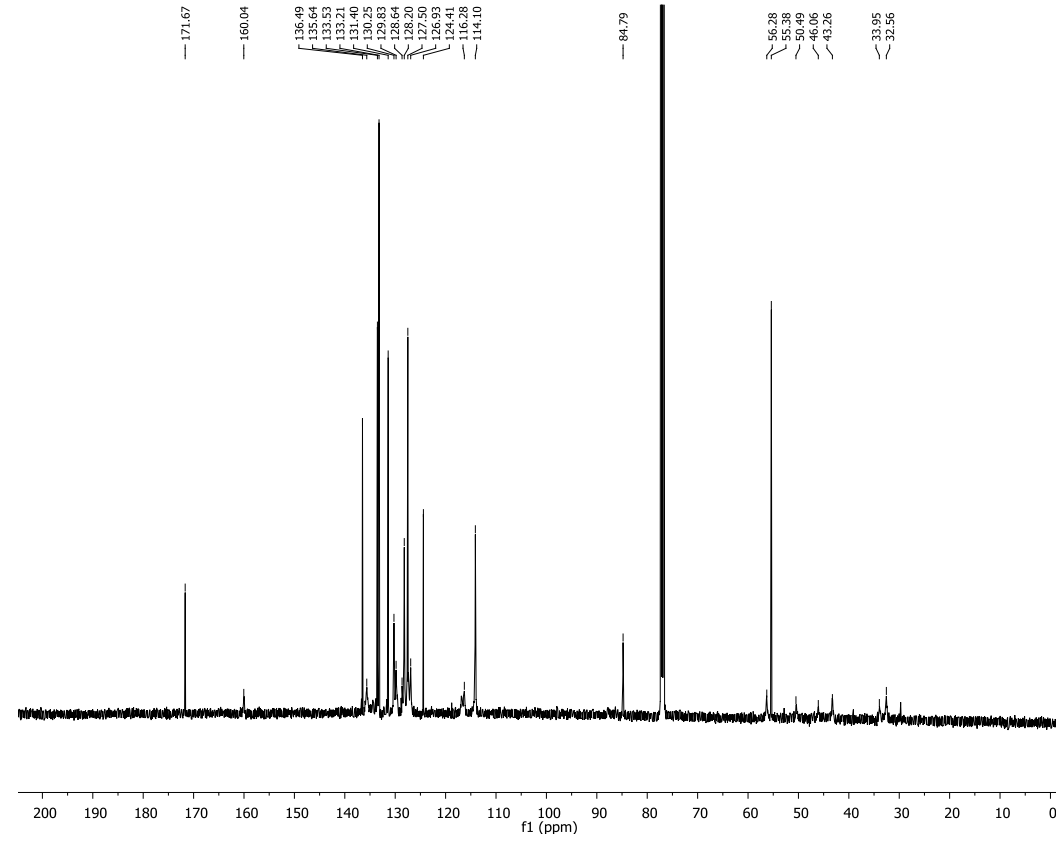

Ph
O
N
F
Br
Ph
4.9h
0.26
1.30
0.49
4.03
7.15
1.20
1.08
2.03
2.06
0.99
0.14
0.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

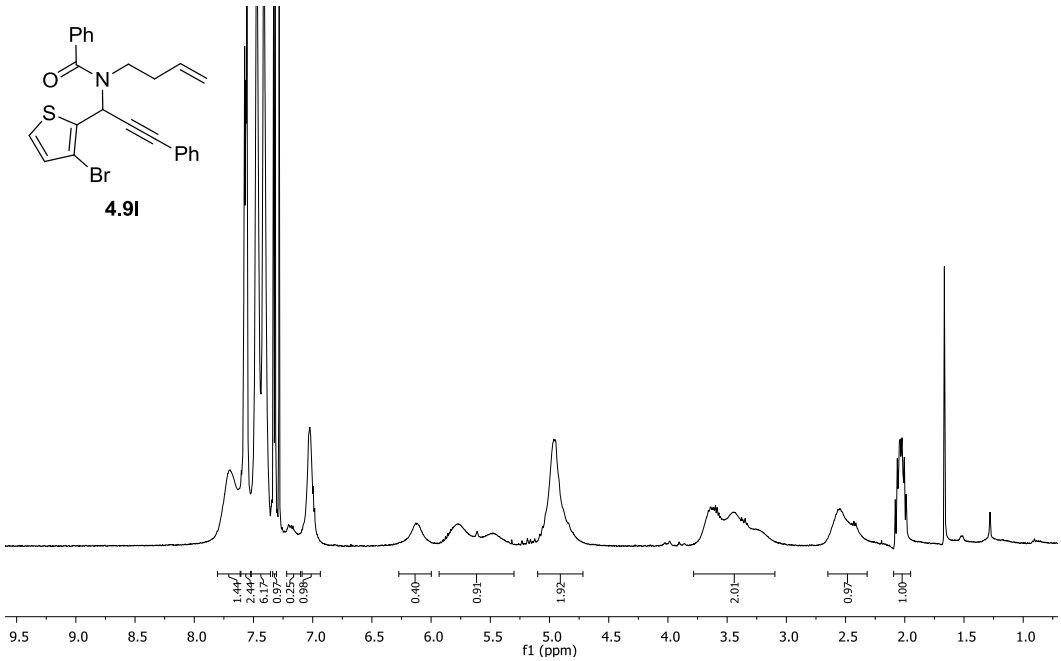

171.75
162.95
162.83
160.97
160.85
136.20
134.83
134.76
131.80
129.85
128.86
128.53
128.47
128.43
128.36
128.31
126.83
118.75
118.55
118.33
117.87
117.69
117.47
117.29
116.58
116.56
85.42
55.97
50.29
46.31
43.28
33.81
32.50
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

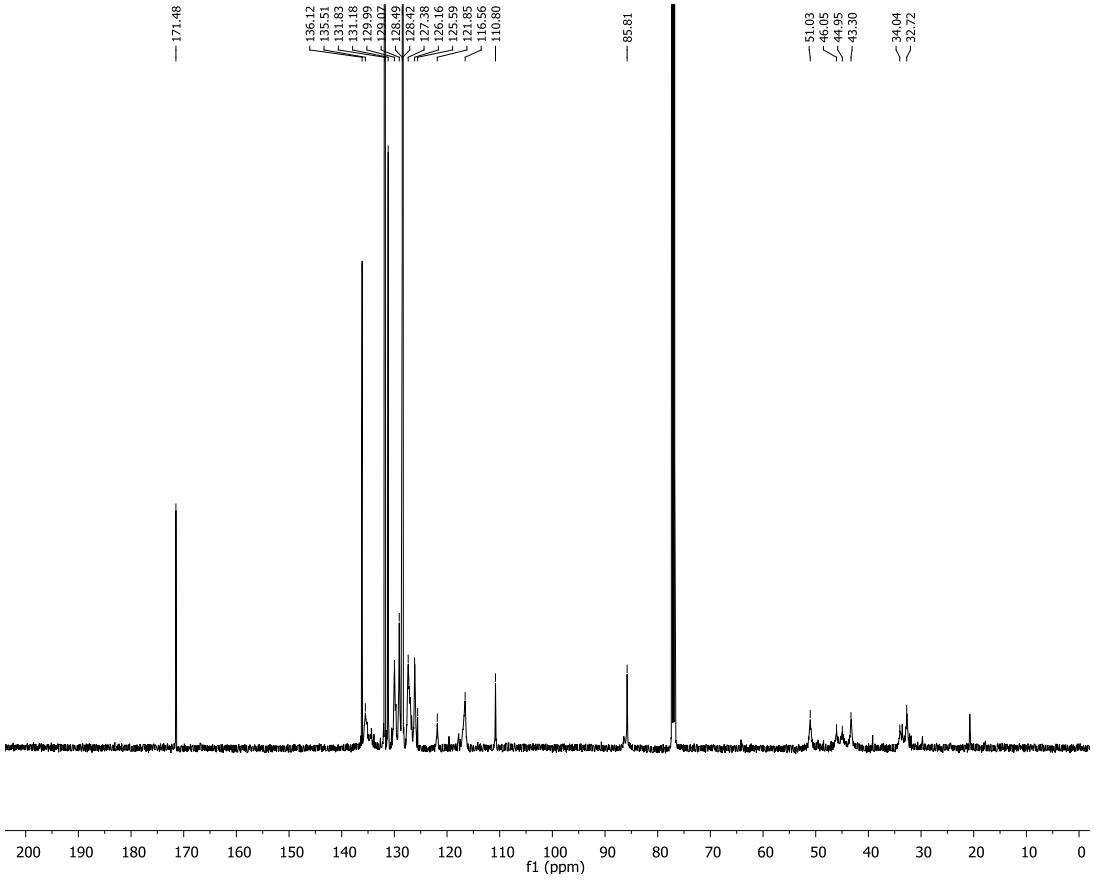

Ph
O
N
Br
F
4.9i
0.89
2.30
2.49
4.87
0.56
1.25
2.00
1.12
1.79
2.30
0.92
1.15
f1 (ppm)

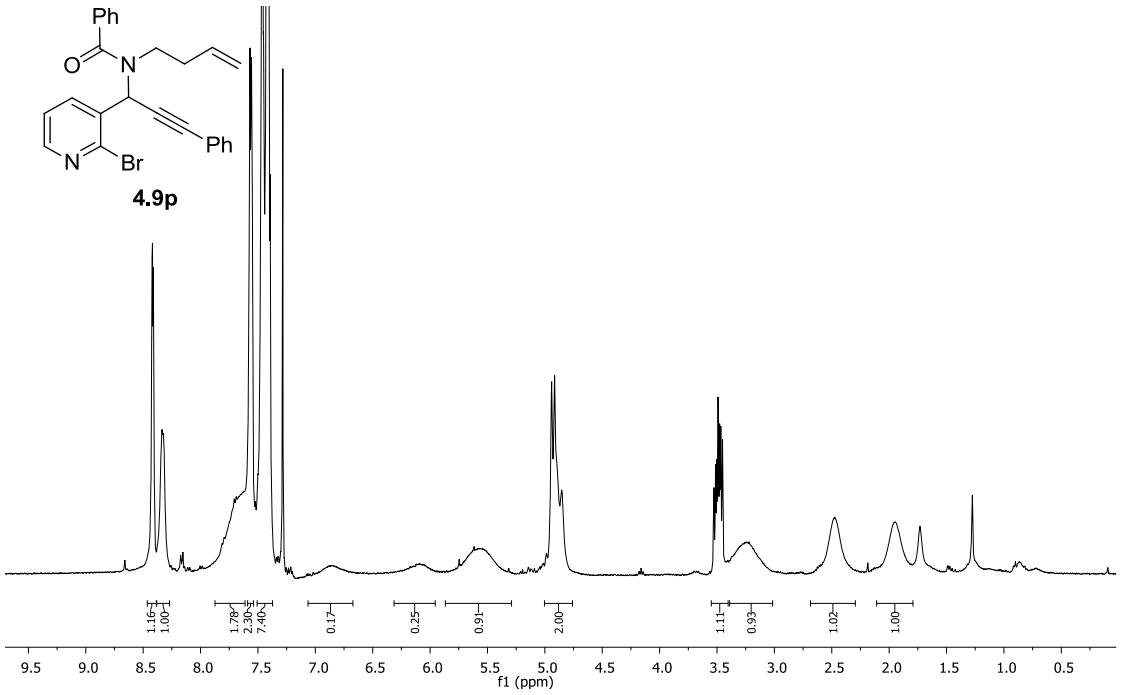

171.68
171.02
163.80
161.81
136.38
133.74
133.67
133.61
131.25
130.35
129.87
129.82
128.60
128.45
128.26
127.55
125.58
116.44
115.91
115.74
85.97
56.13
50.15
46.06
43.34
33.88
32.58
f1 (ppm)

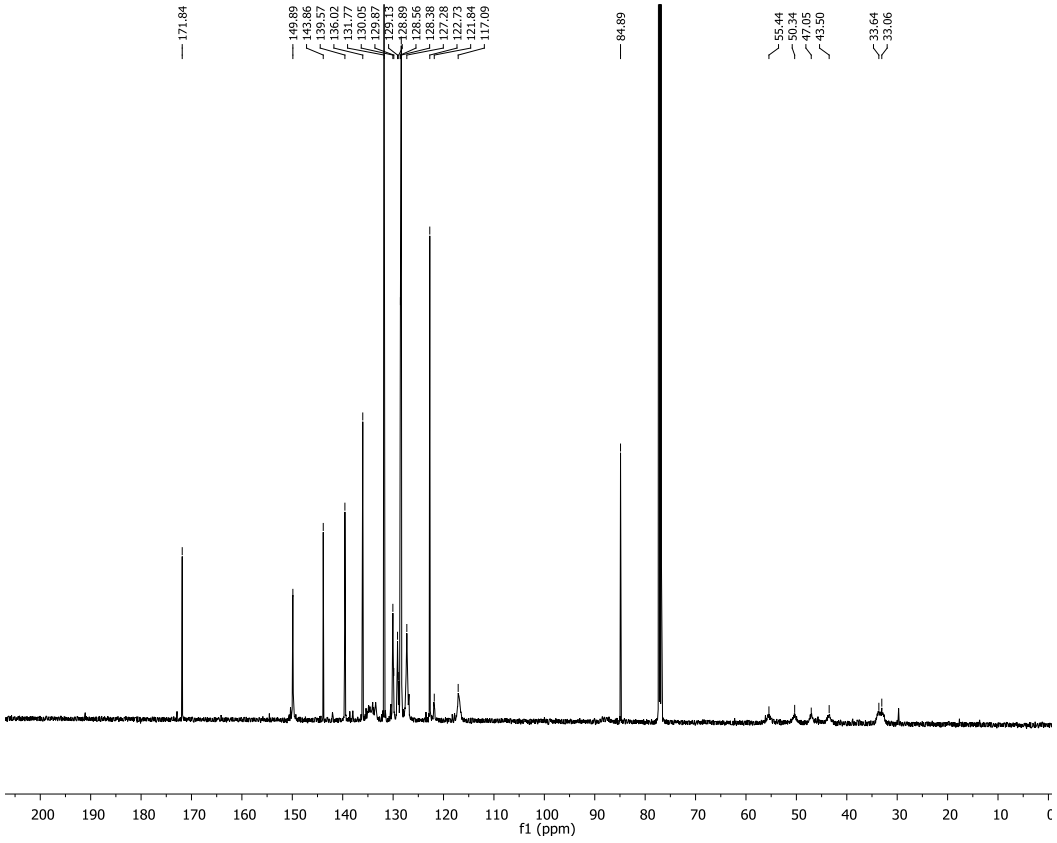

Ph
O
N
Br
O
4.9j
0.99
1.03
1.67
2.44
4.14
0.96
0.26
1.98
0.35
0.81
1.80
3.04
1.81
0.90
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

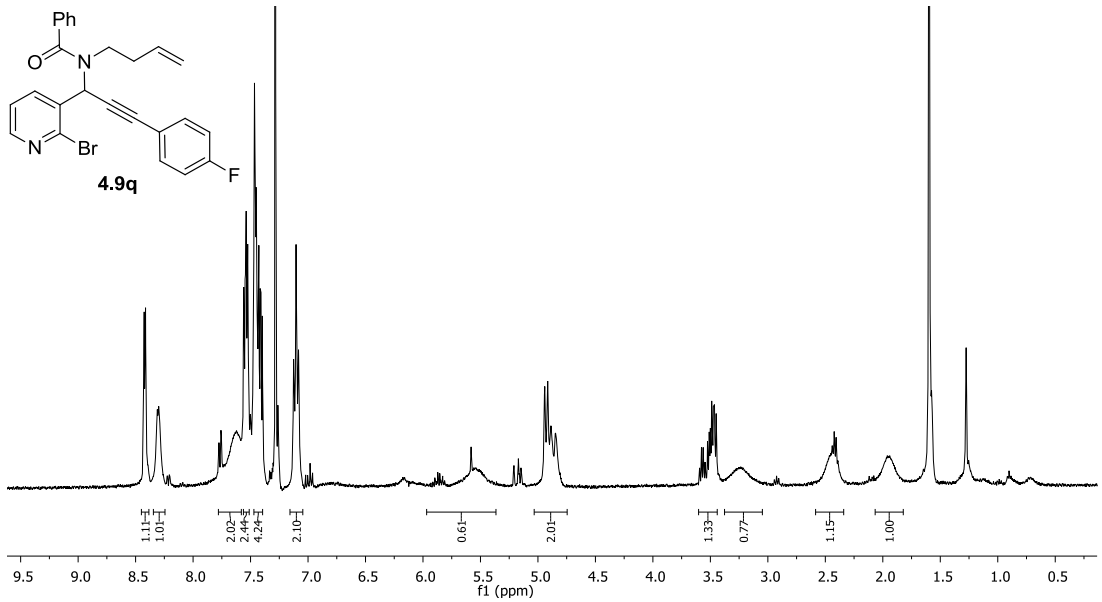

171.67
160.04
136.49
135.64
133.53
133.21
131.40
130.25
129.83
128.64
128.20
127.50
126.93
124.41
116.28
114.10
84.79
56.28
55.38
50.49
46.06
43.26
33.95
32.56
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

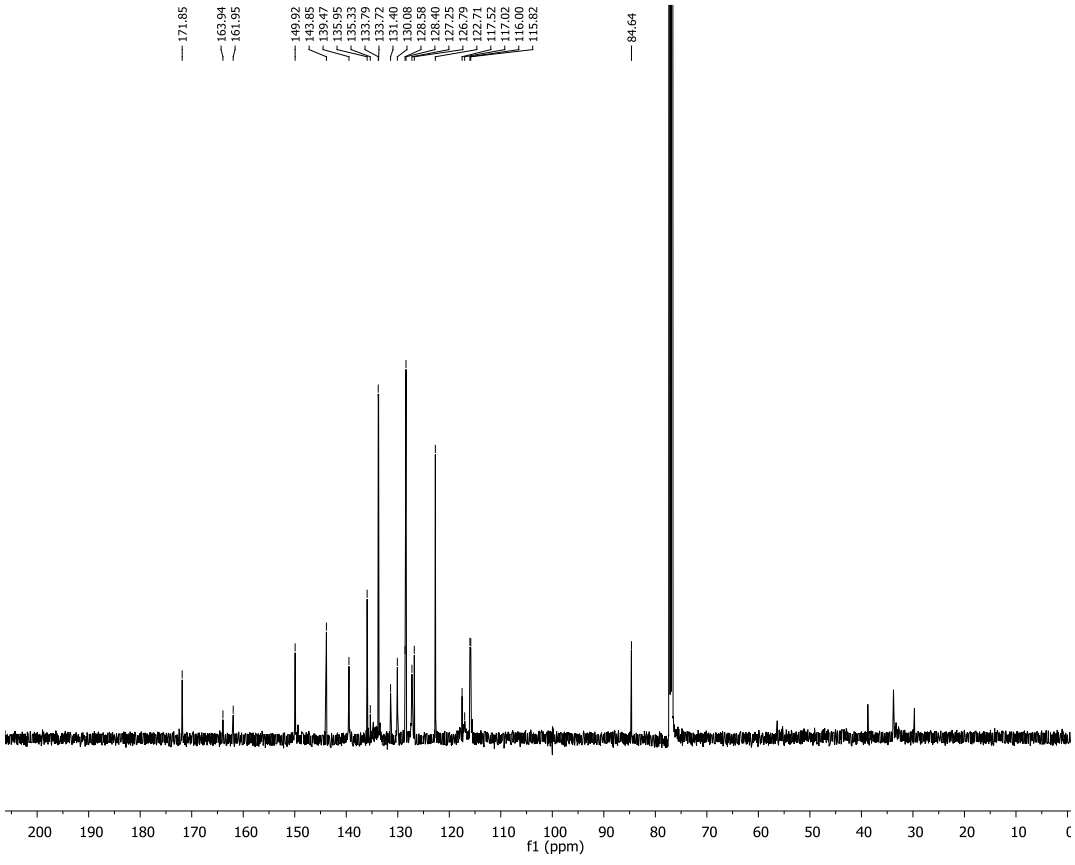

Ph
O
N
S
Br
Ph
4.9l
1.44
2.44
6.17
0.97
0.25
0.98
0.40
0.91
1.92
2.01
0.97
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

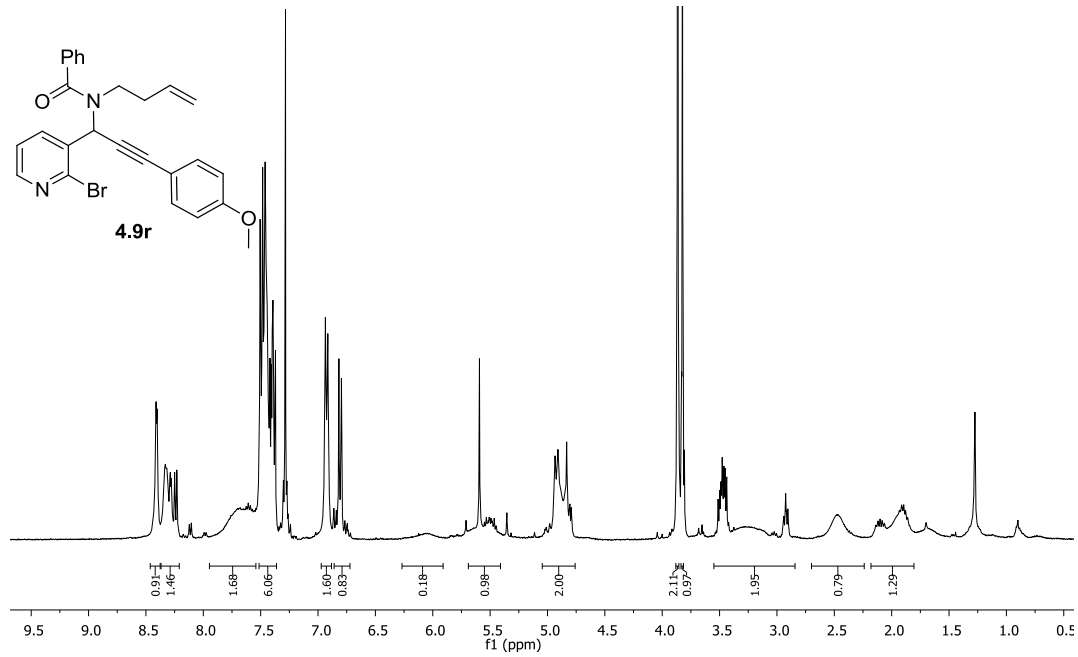

171.48
136.12
135.51
131.83
131.18
129.99
129.07
128.49
128.42
127.38
126.16
125.59
121.85
116.56
110.80
85.81
51.03
46.05
44.95
43.30
34.04
32.72
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

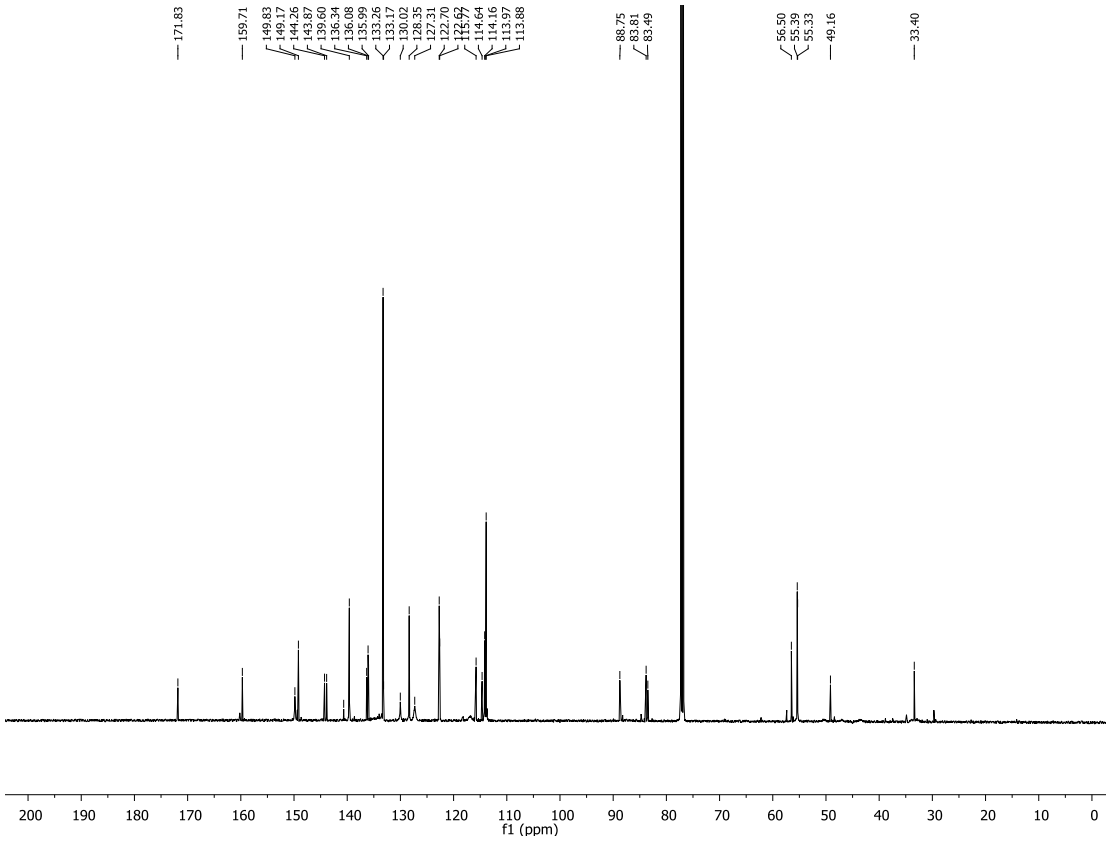

Ph
O
N
Ph
N
Br
4.9p
1.16
1.00
1.78
2.30
7.40
0.17
0.25
0.91
2.00
1.11
0.93
1.02
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

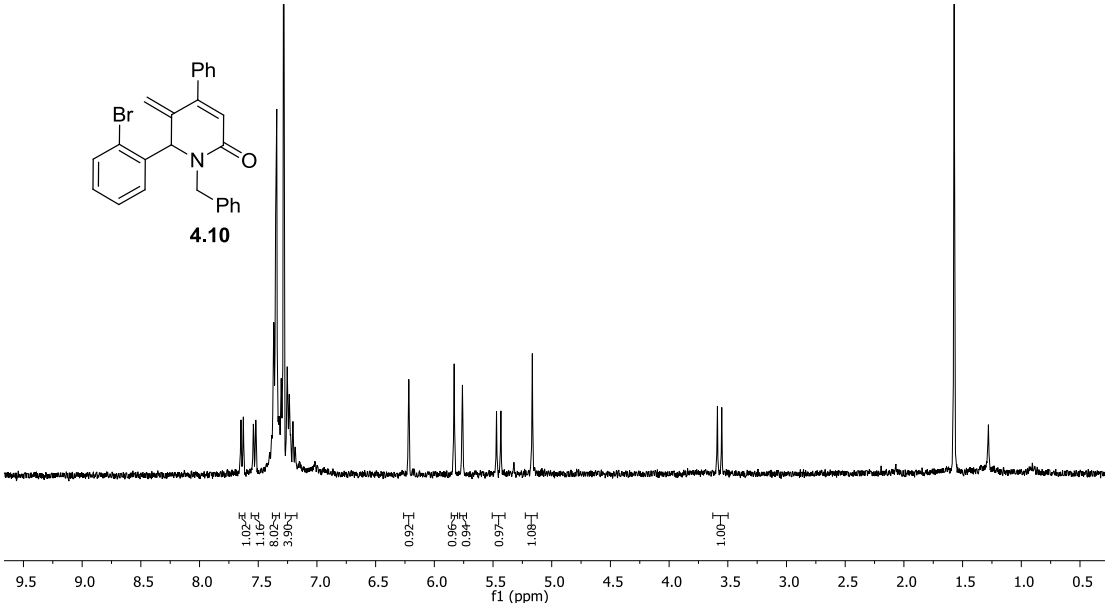

171.84
149.89
143.86
139.57
136.02
131.77
130.05
129.67
128.93
128.89
128.55
128.38
127.28
122.73
121.84
117.09
84.89
55.44
50.34
47.05
43.50
33.64
33.06
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

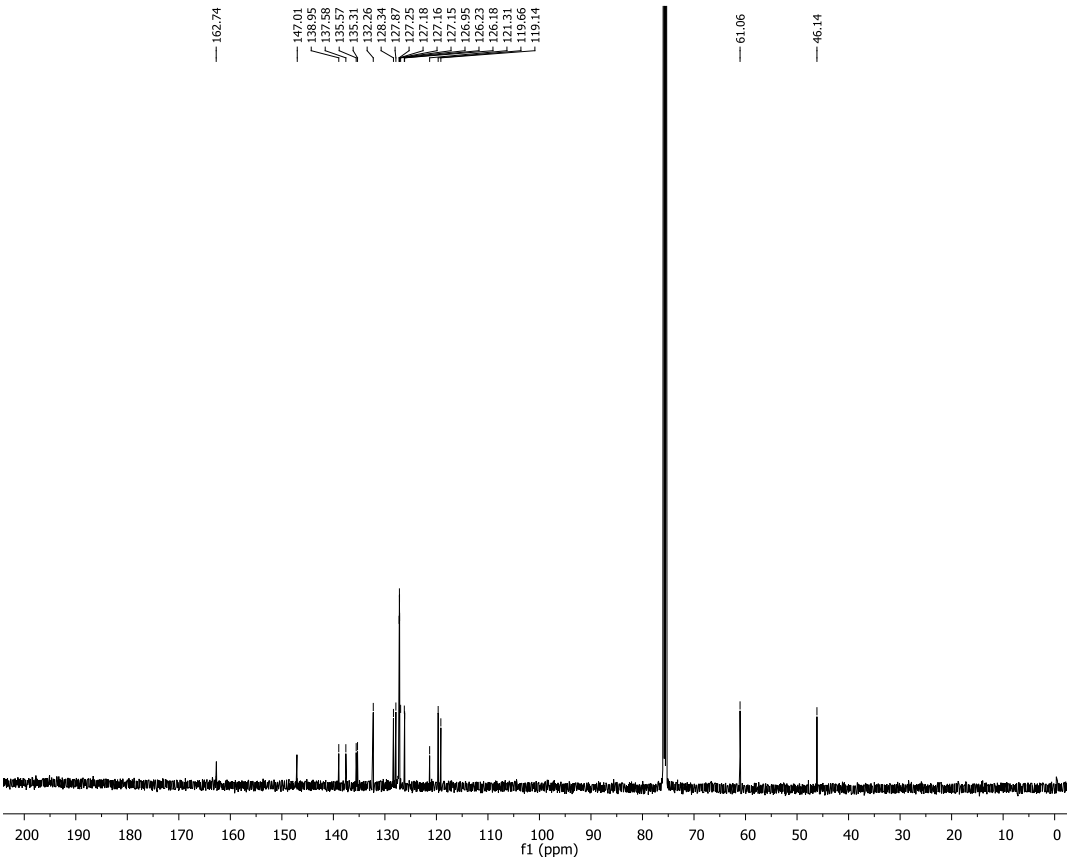

Ph
O
N
N
Br
F
4.9q
1.11
1.01
2.02
2.44
4.24
2.10
0.61
2.01
1.33
0.77
1.15
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

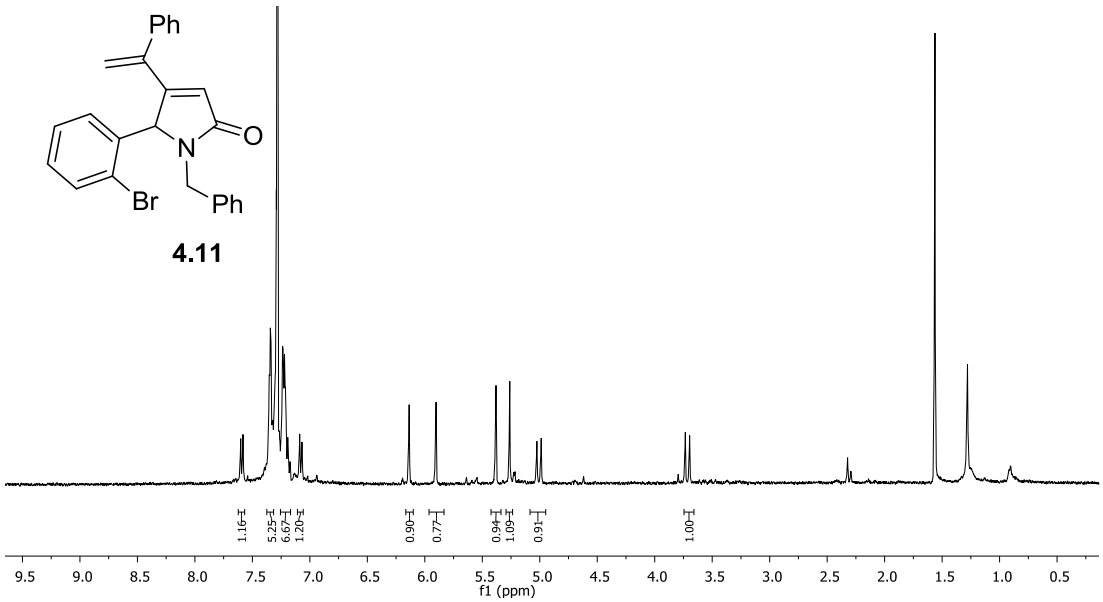

171.85
163.94
161.95
149.92
143.85
139.47
135.95
135.33
133.79
133.72
131.40
130.08
128.58
128.40
127.25
126.79
122.71
117.52
117.02
116.00
115.82
84.64
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Ph
O
N
N
Br
O
4.9r
0.91
1.46
1.68
6.06
1.60
0.83
0.18
0.98
2.00
2.11
0.97
1.95
0.79
1.29
f1 (ppm)

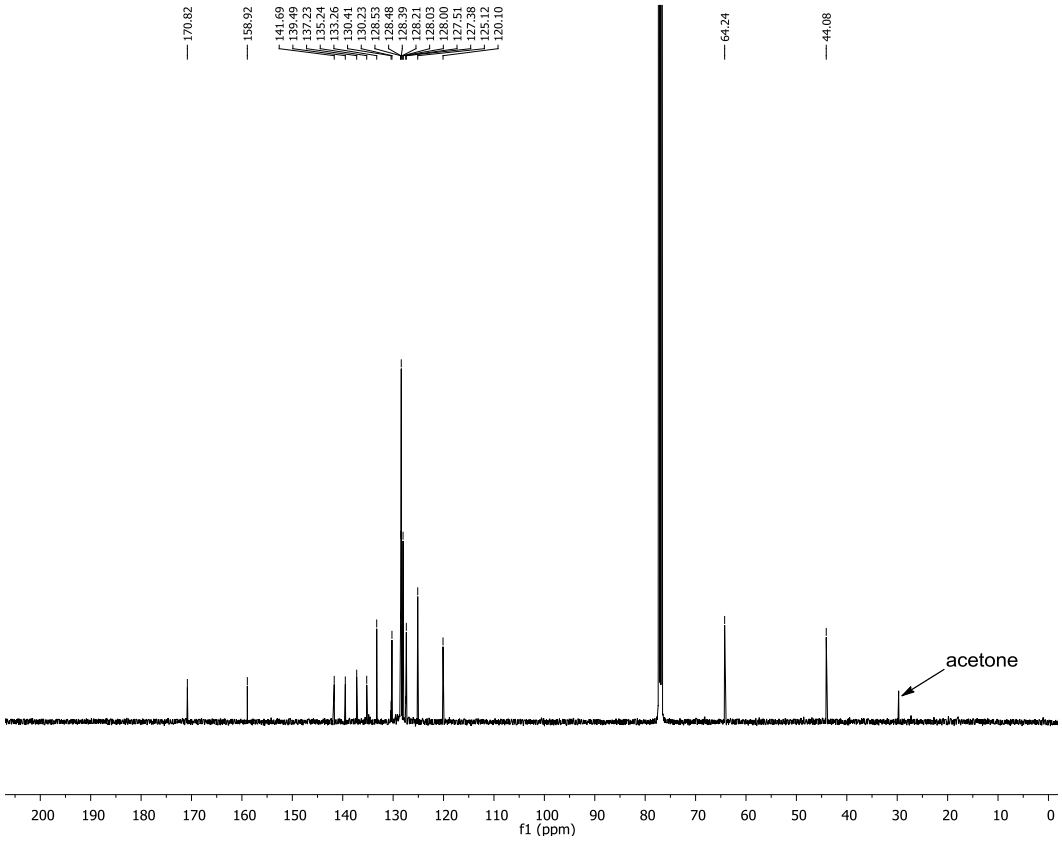

171.83
159.71
149.83
149.17
144.26
143.87
139.60
136.34
136.08
135.99
133.26
133.17
130.02
128.35
122.31
122.20
115.97
114.64
114.16
113.97
113.88
88.75
83.81
83.49
56.50
55.39
55.33
49.16
33.40
f1 (ppm)

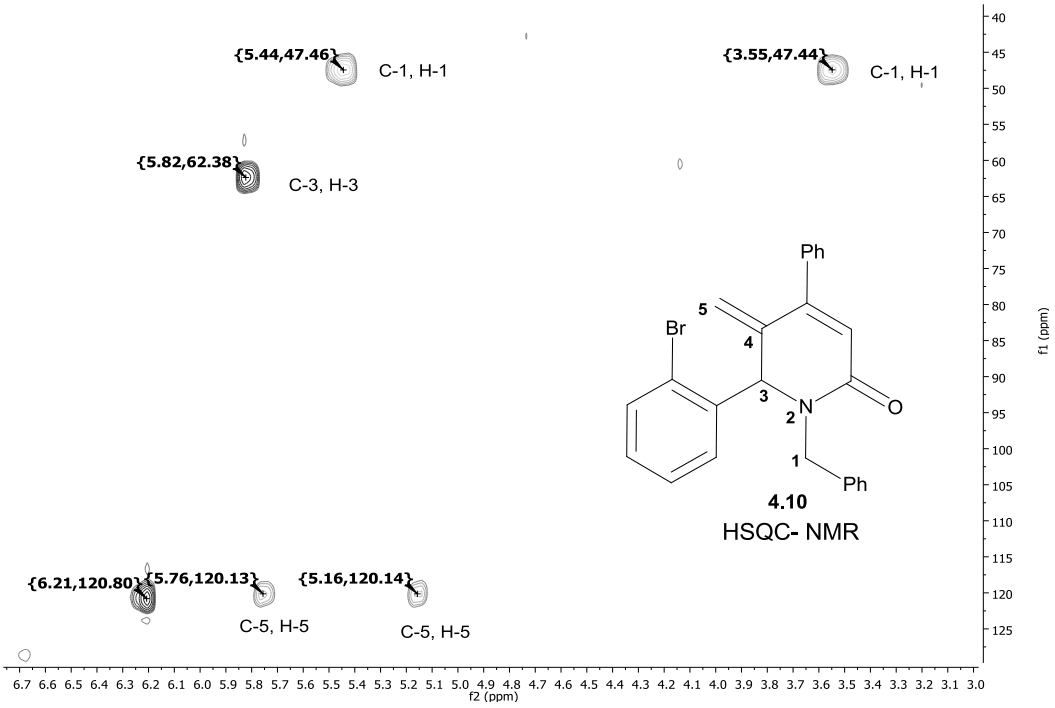

Ph
Br
N
O
Ph
4.10
1.02
1.16
8.02
3.96
0.92
0.96
0.94
0.97
1.08
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


162.74
147.01
138.95
137.58
135.57
135.31
132.26
128.34
127.87
127.25
127.18
127.16
127.15
126.95
126.23
126.18
121.31
119.66
119.14
61.06
46.14
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

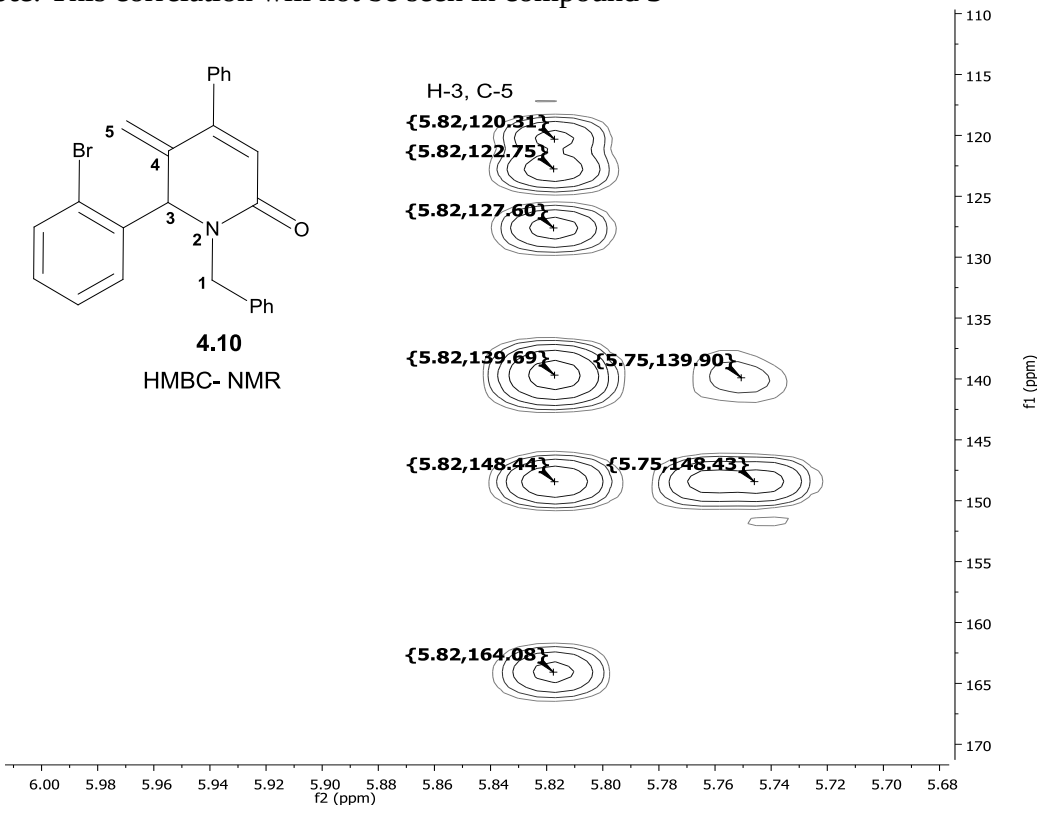

Ph
O
N
Br
Ph
1.16
5.25
6.67
1.20
0.90
0.77
0.94
1.09
0.91
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

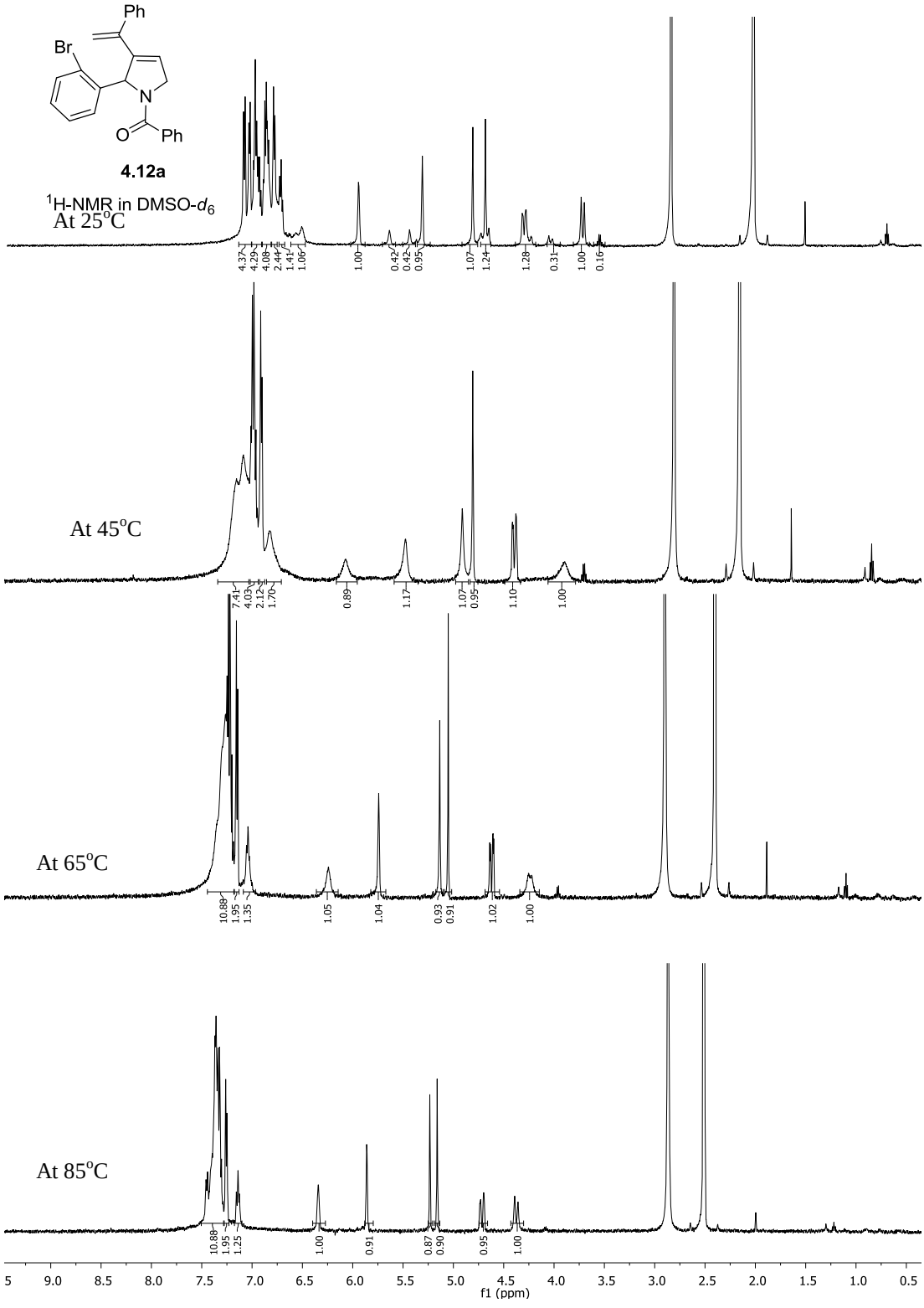
4.11

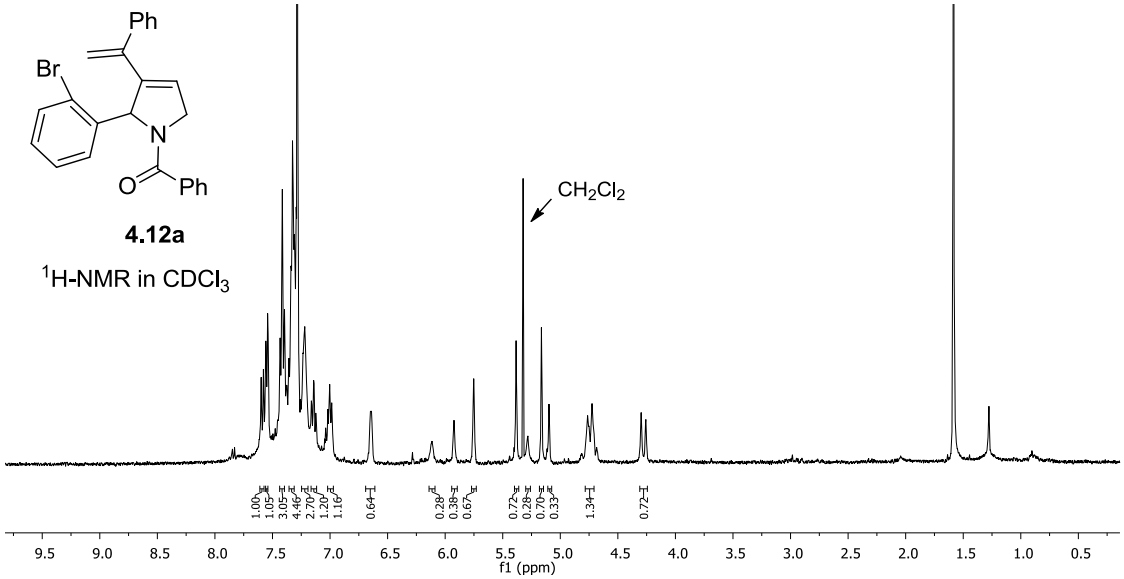

170.82
158.92
141.69
139.49
137.23
135.24
133.26
130.41
130.23
128.53
128.48
128.39
128.21
128.03
128.00
127.51
127.38
125.12
120.10
64.24
44.08
acetone
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

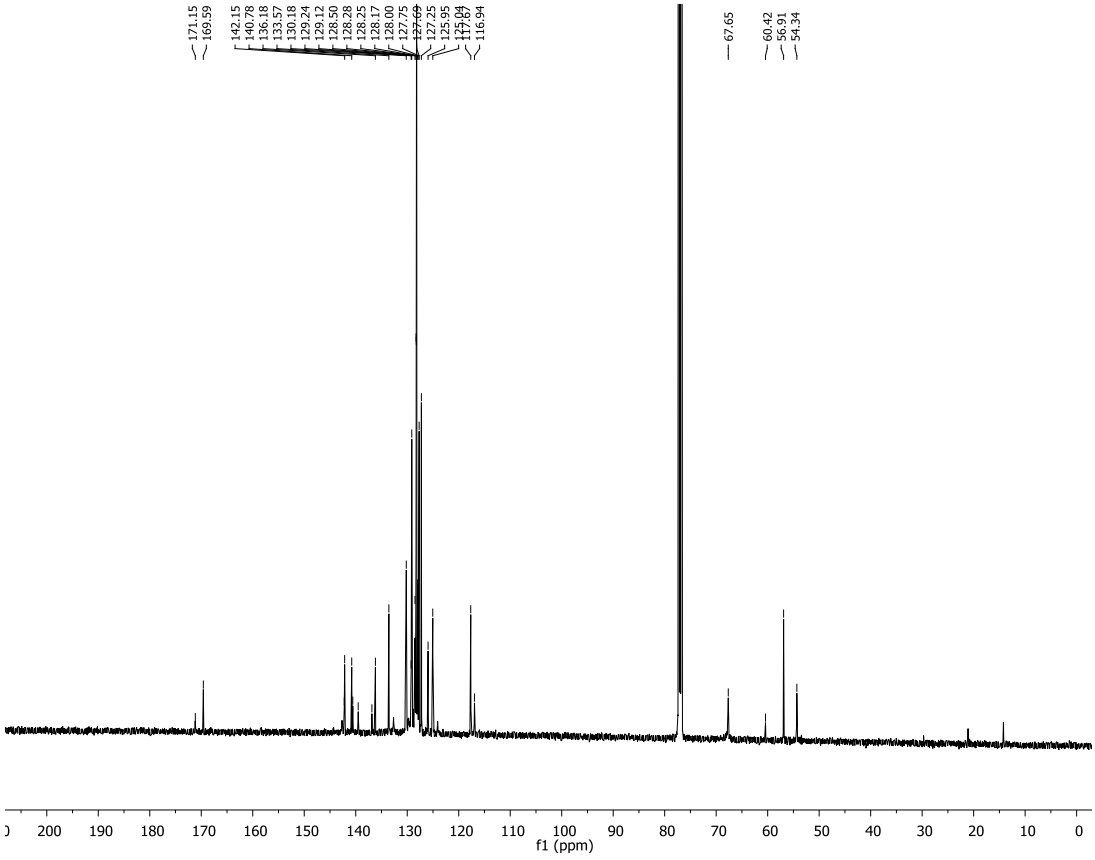


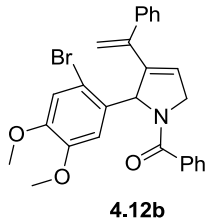
HMBC-NMR: Long range correlation seen between H-3 and C-5.
Note: This correlation will not be seen in compound **3**




Ph
Br
N
O
Ph
4.12a
^{1}H-NMR in DMSO-d_6
At 25°C
At 45°C
At 65°C
At 85°C
f1 (ppm)

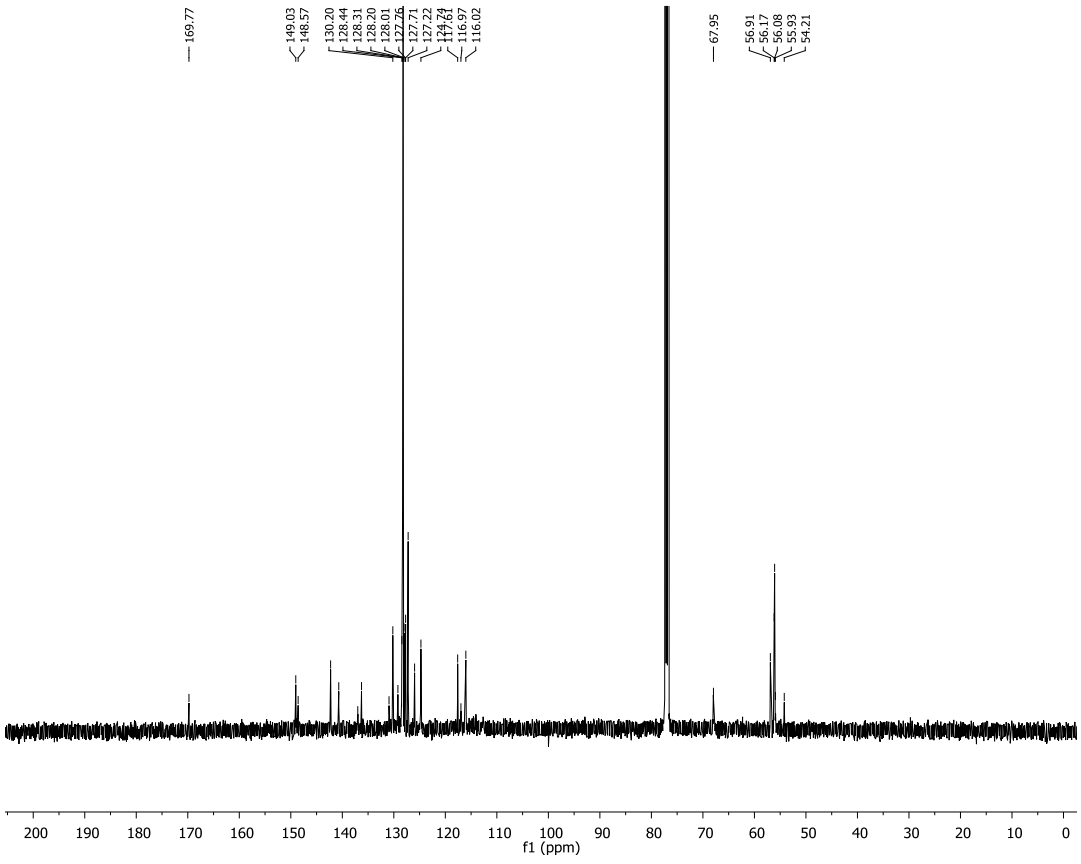

Ph
Br
N
O
Ph
4.12a
^{1}H-NMR in CDCl$_3$
CH_2Cl_2
1.00
1.05
3.05
4.46
2.70
1.20
1.16
0.64
0.28
0.38
0.67
0.72
0.28
0.70
0.33
1.34
0.72
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

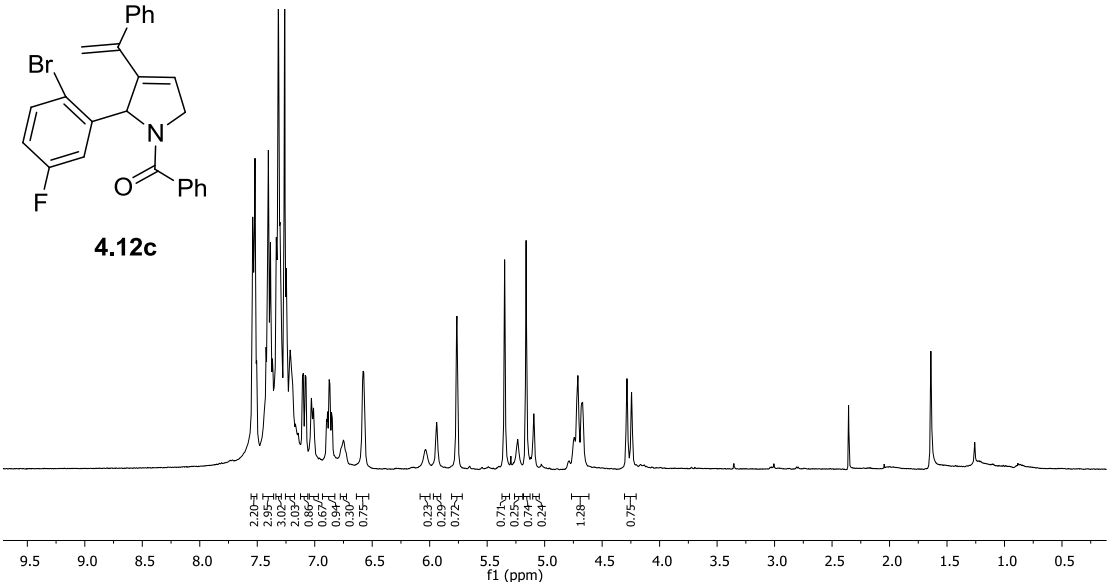

171.15
169.59
142.15
140.78
136.18
133.57
130.18
129.24
129.12
128.50
128.28
128.25
128.17
128.00
127.75
127.69
127.25
125.95
117.64
116.94
67.65
60.42
56.91
54.34
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
Br
N
O
O
O
Ph

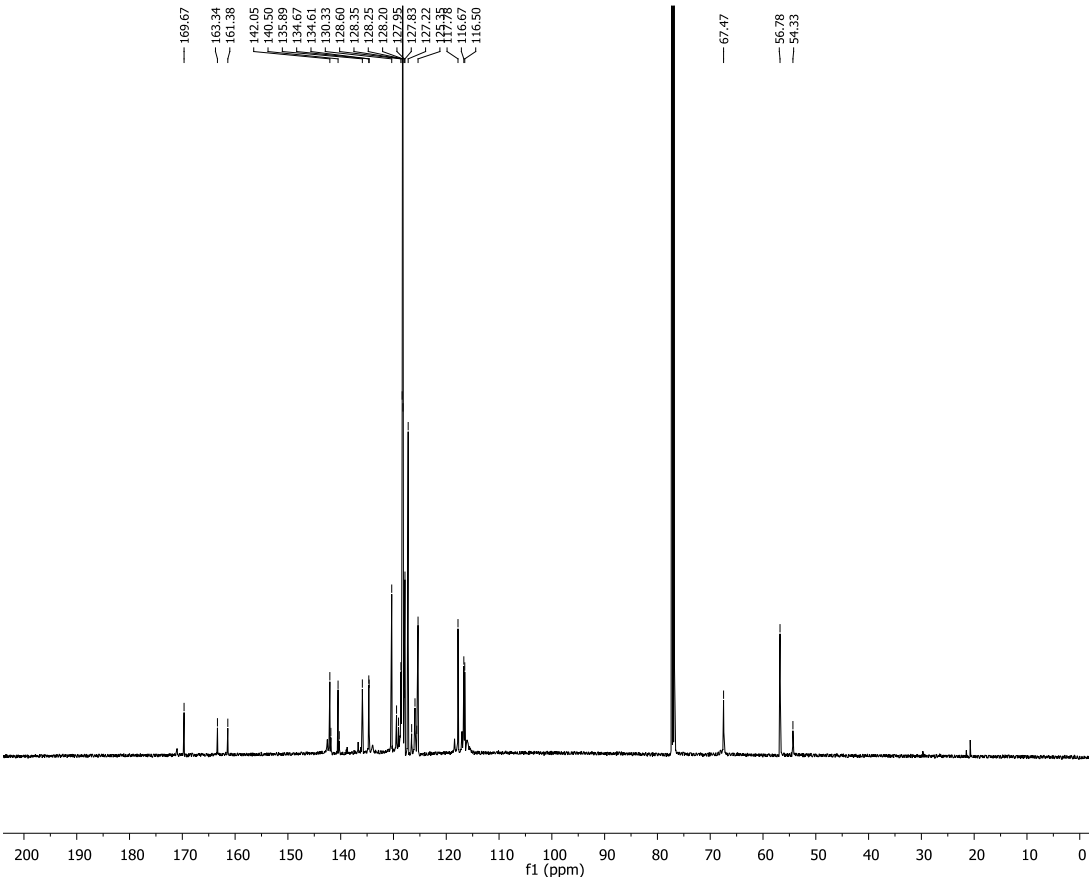
4.12b

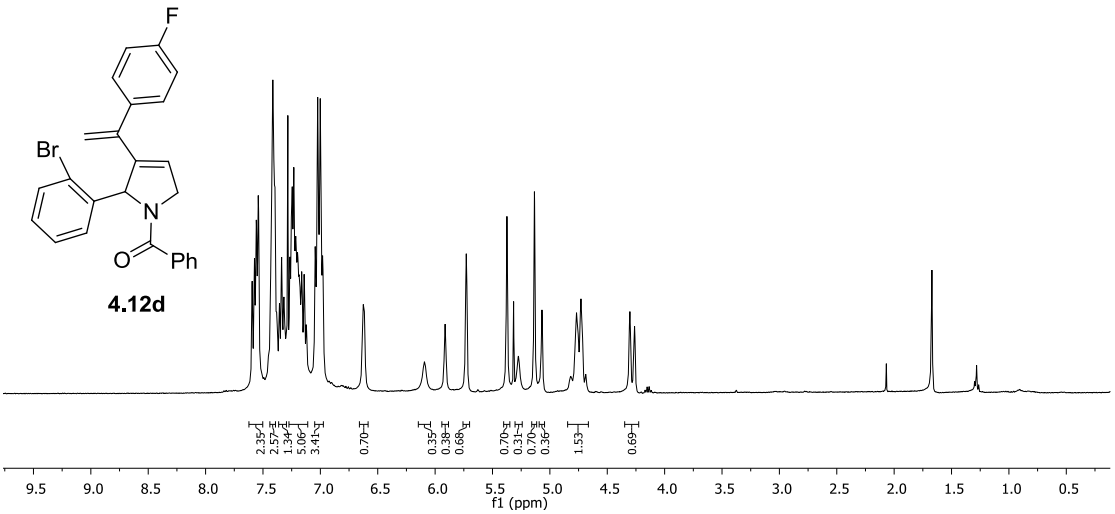
1.54
2.65
4.39
1.68
1.62
0.66
0.29
0.67
0.44
0.64
0.70
0.29
0.70
0.40
1.57
0.64
2.17
2.09
1.68
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

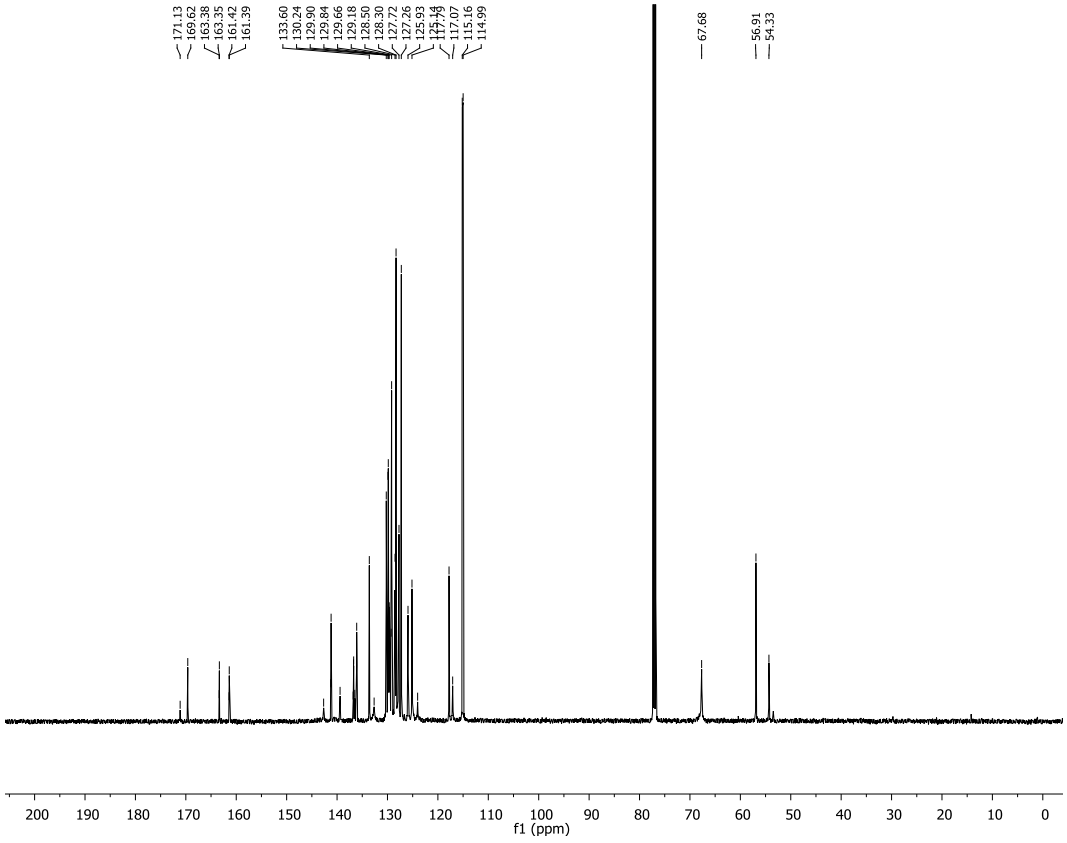

169.77
149.03
148.57
130.20
128.44
128.31
128.20
128.01
127.26
127.71
127.22
124.24
117.61
116.97
116.02
67.95
56.91
56.17
56.08
55.93
54.21
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

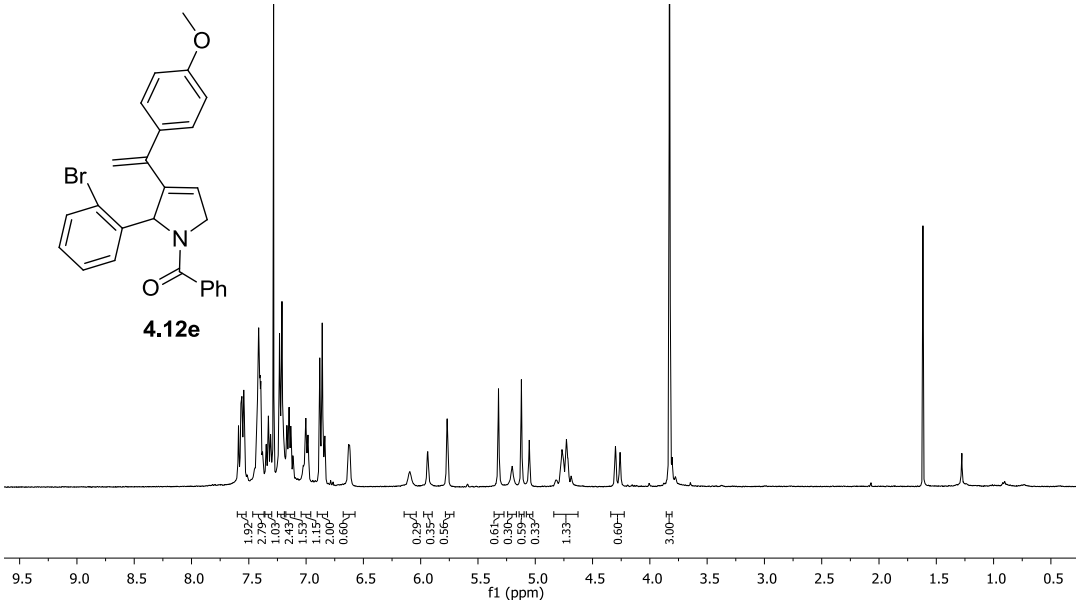

Ph
Br
N
O
Ph
F
2.20
2.95
3.02
2.03
0.86
0.67
0.94
0.30
0.75
0.23
0.29
0.72
0.71
0.25
0.74
0.24
1.28
0.75
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

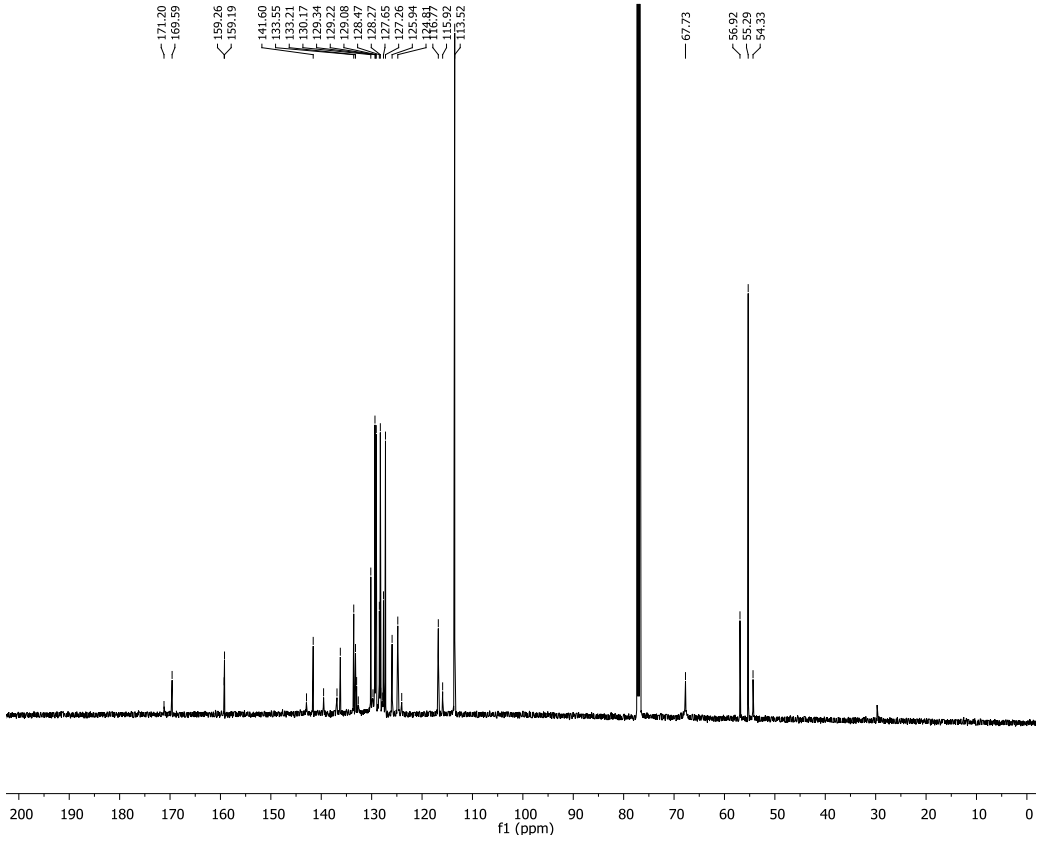
4.12c

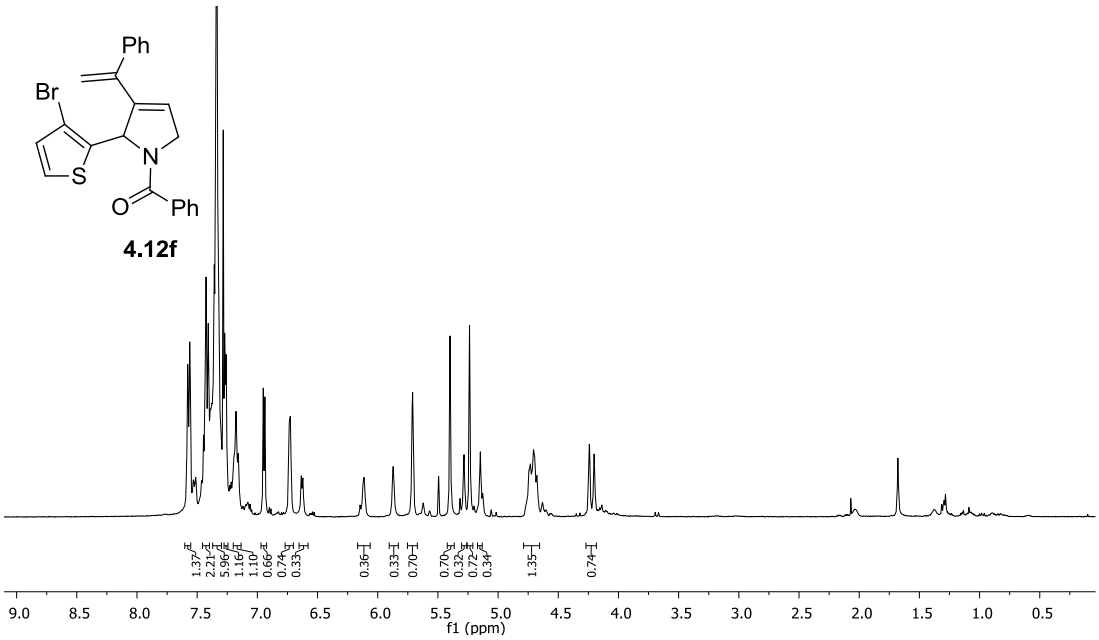

169.67
163.34
161.38
142.05
140.50
135.89
134.67
134.61
130.33
128.60
128.35
128.25
128.20
127.95
127.83
127.22
125.35
117.78
116.67
116.50
67.47
56.78
54.33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

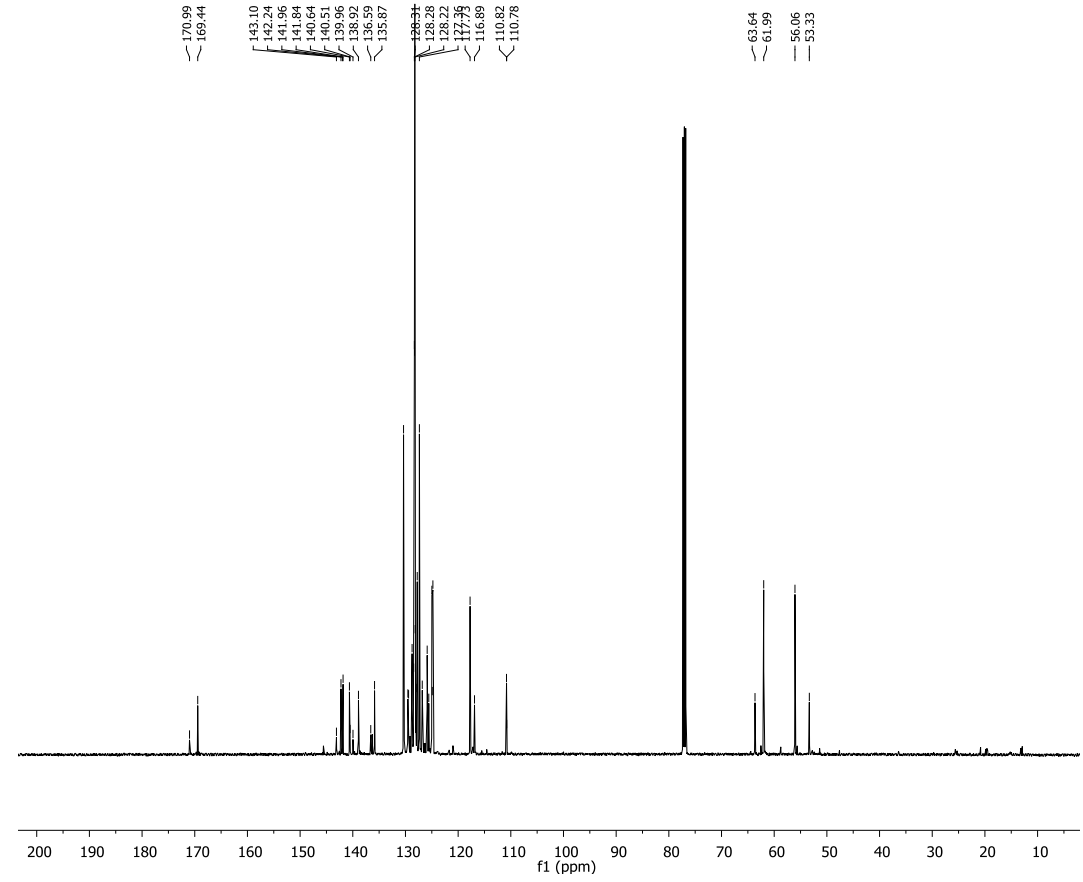

F
Br
N
O
Ph
4.12d
2.35
2.57
1.34
5.06
3.41
0.70
0.35
0.38
0.68
0.70
0.31
0.70
0.36
1.53
0.69
f1 (ppm)

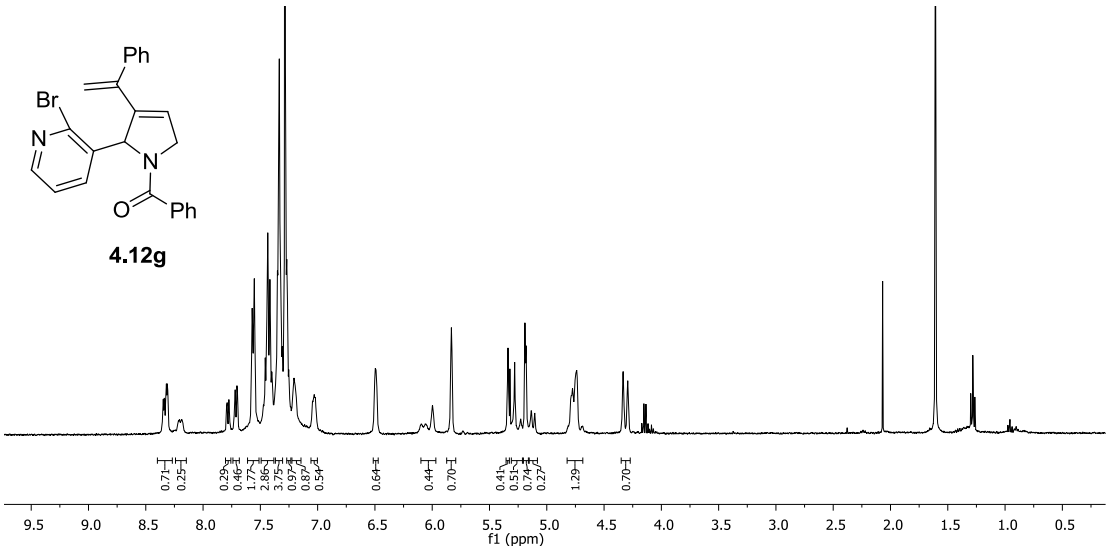

171.13
169.62
163.38
163.35
161.42
161.39
133.60
130.24
129.90
129.84
129.66
129.18
128.50
128.30
127.72
127.26
125.93
117.07
115.16
114.99
67.68
56.91
54.33
f1 (ppm)

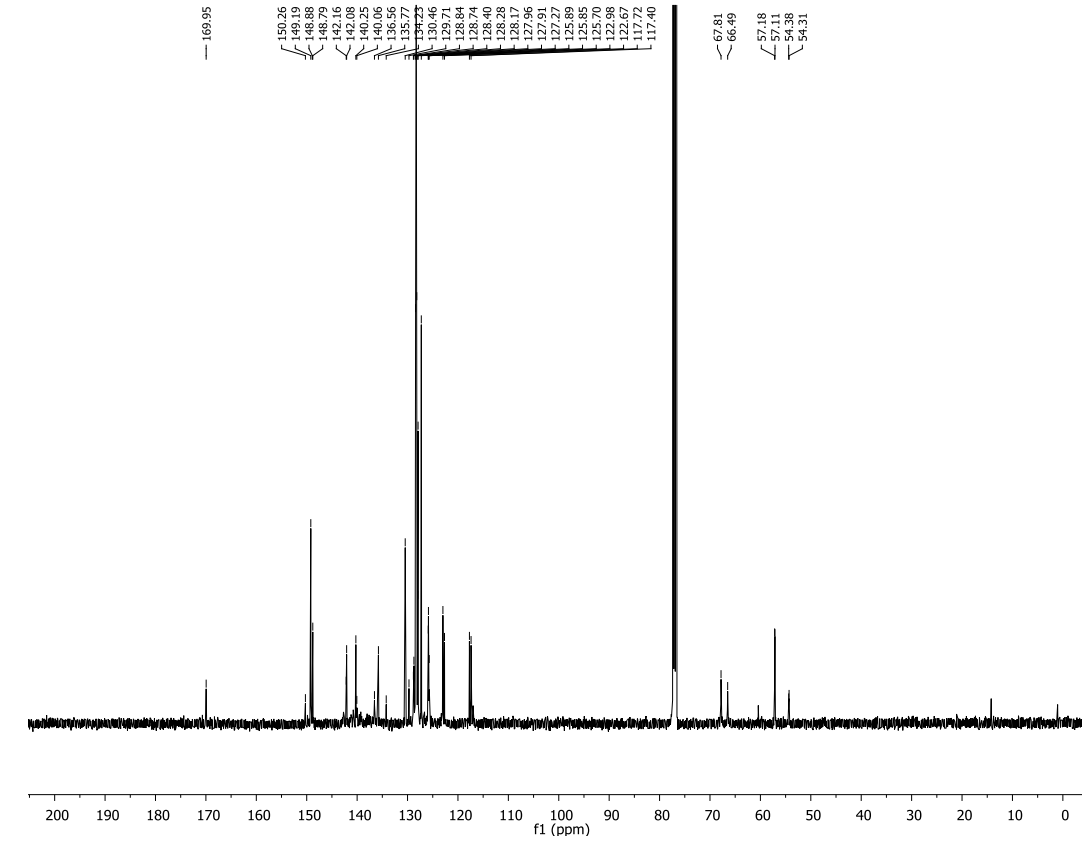

O
Br
N
O
Ph
4.12e
1.92
2.79
1.03
2.49
1.37
1.15
2.00
0.60
0.29
0.35
0.56
0.61
0.30
0.59
0.33
1.33
0.60
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

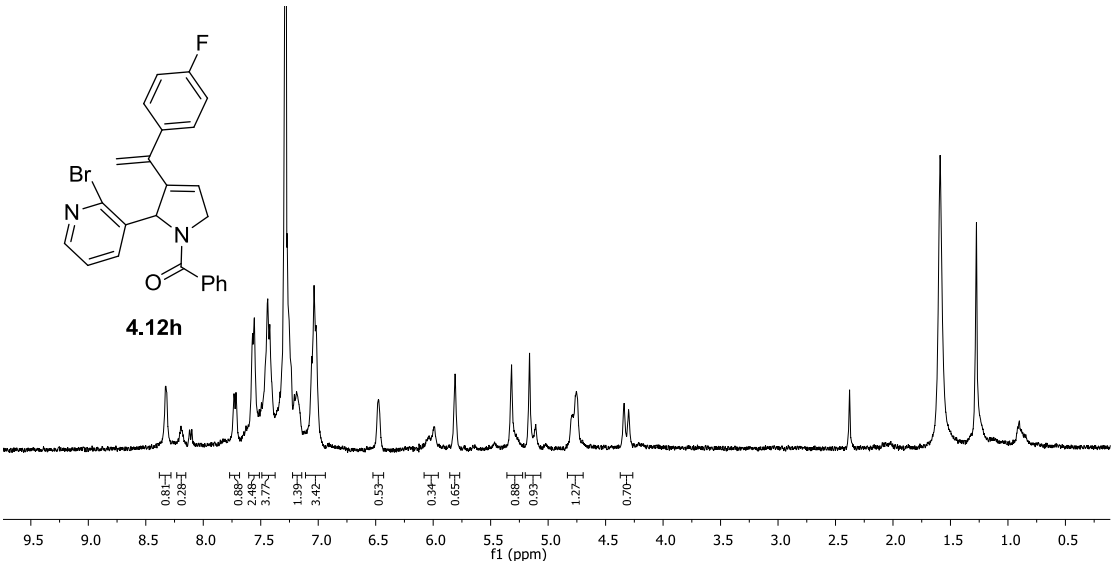

171.20
169.59
159.26
159.19
141.60
133.55
133.21
130.17
129.34
129.22
129.08
128.47
128.27
127.65
127.26
125.94
115.92
113.52
67.73
56.92
55.29
54.33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

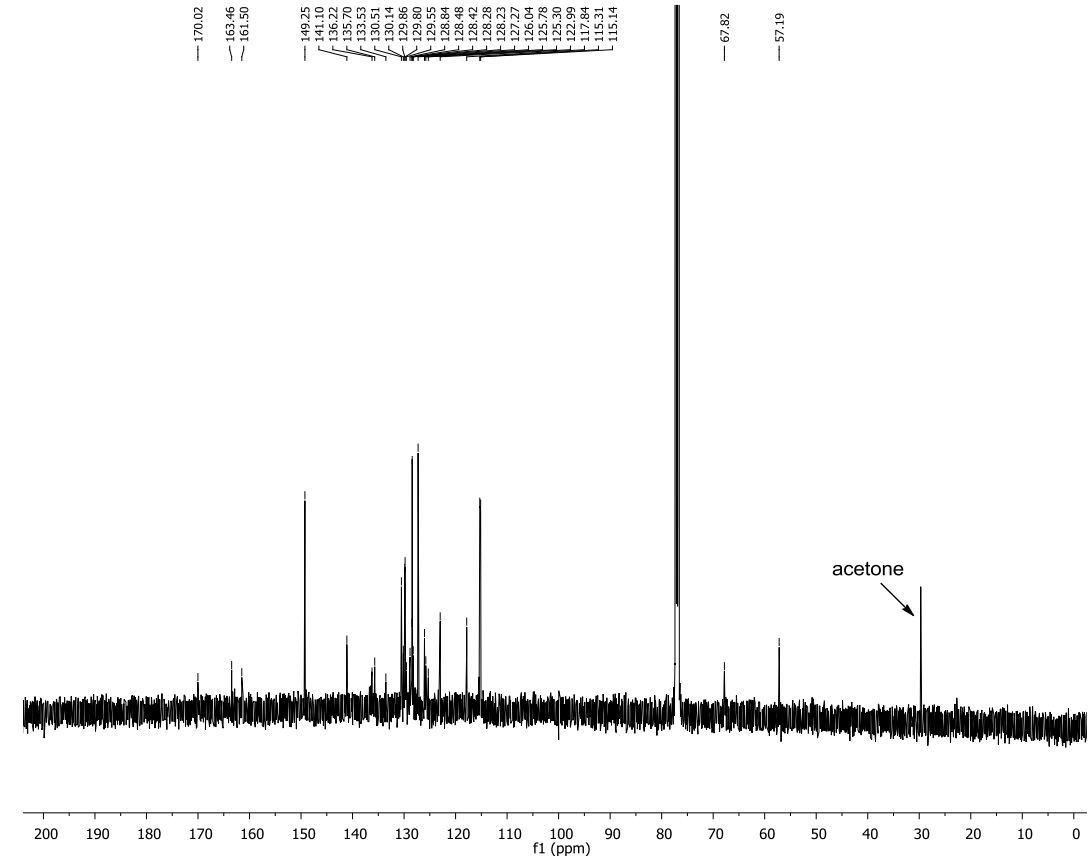

Ph
Br
N
S
O
Ph
4.12f
1.37
2.21
5.96
1.16
1.10
0.66
0.74
0.33
0.36
0.33
0.70
0.70
0.32
0.72
0.34
1.35
0.74
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

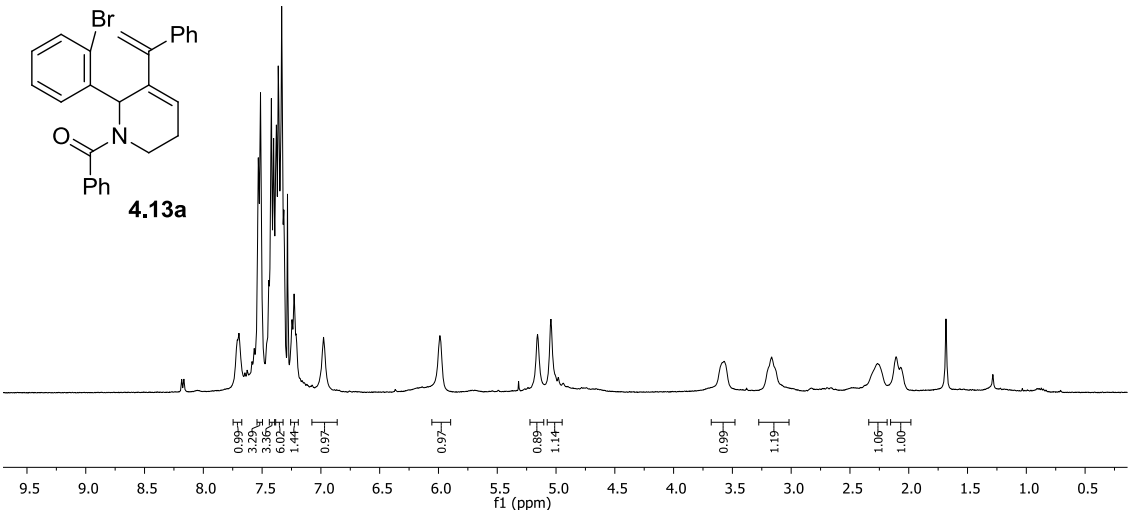

170.99
169.44
143.10
142.24
141.96
141.84
140.64
140.51
139.96
138.92
136.59
135.87
128.31
128.28
128.22
127.36
117.33
116.89
110.82
110.78
63.64
61.99
56.06
53.33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

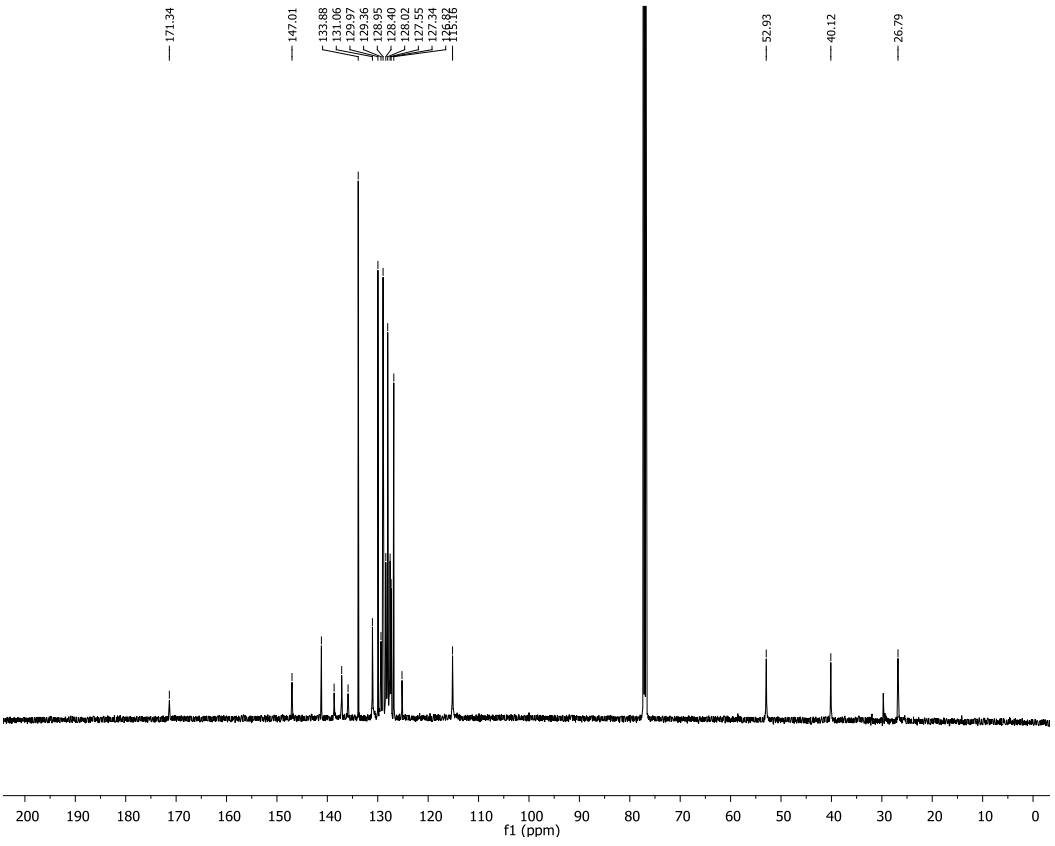

Ph
Br
N
N
O
Ph
4.12g
0.71
0.25
0.29
0.46
1.77
2.86
3.75
0.97
0.87
0.54
0.64
0.44
0.70
0.41
0.51
0.74
0.27
1.29
0.70
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

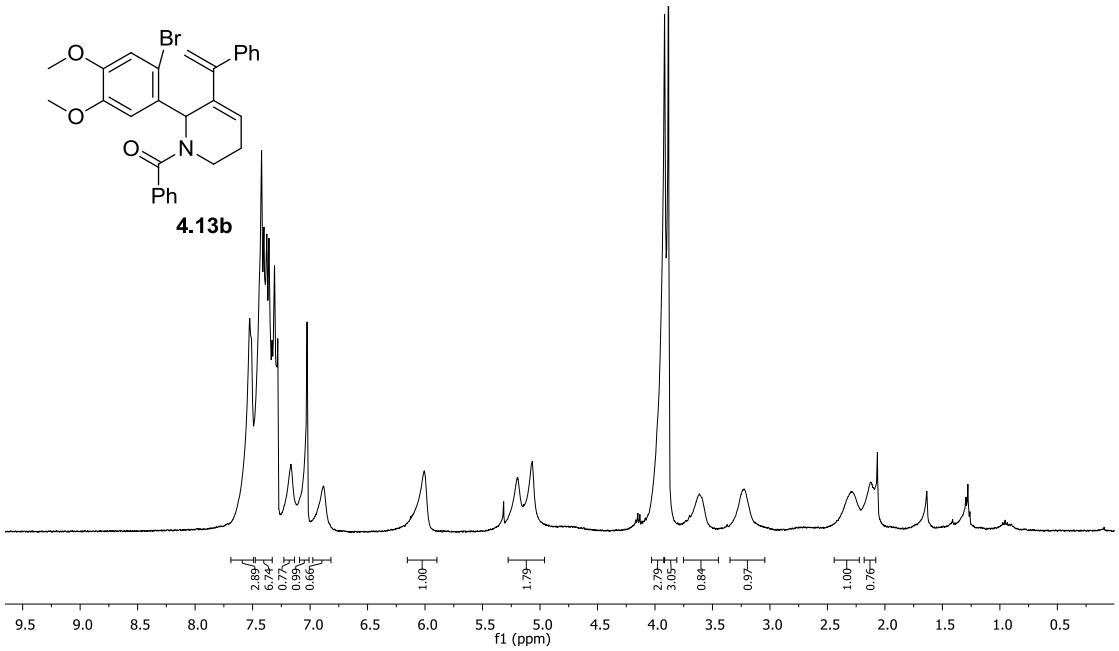

169.95
150.26
149.19
148.88
148.79
142.16
142.08
140.25
140.06
136.56
135.77
134.23
130.46
129.71
128.84
128.74
128.40
128.28
128.17
127.96
127.91
127.27
125.89
125.55
125.70
122.98
122.67
117.72
117.40
67.81
66.49
57.18
57.11
54.38
54.31
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

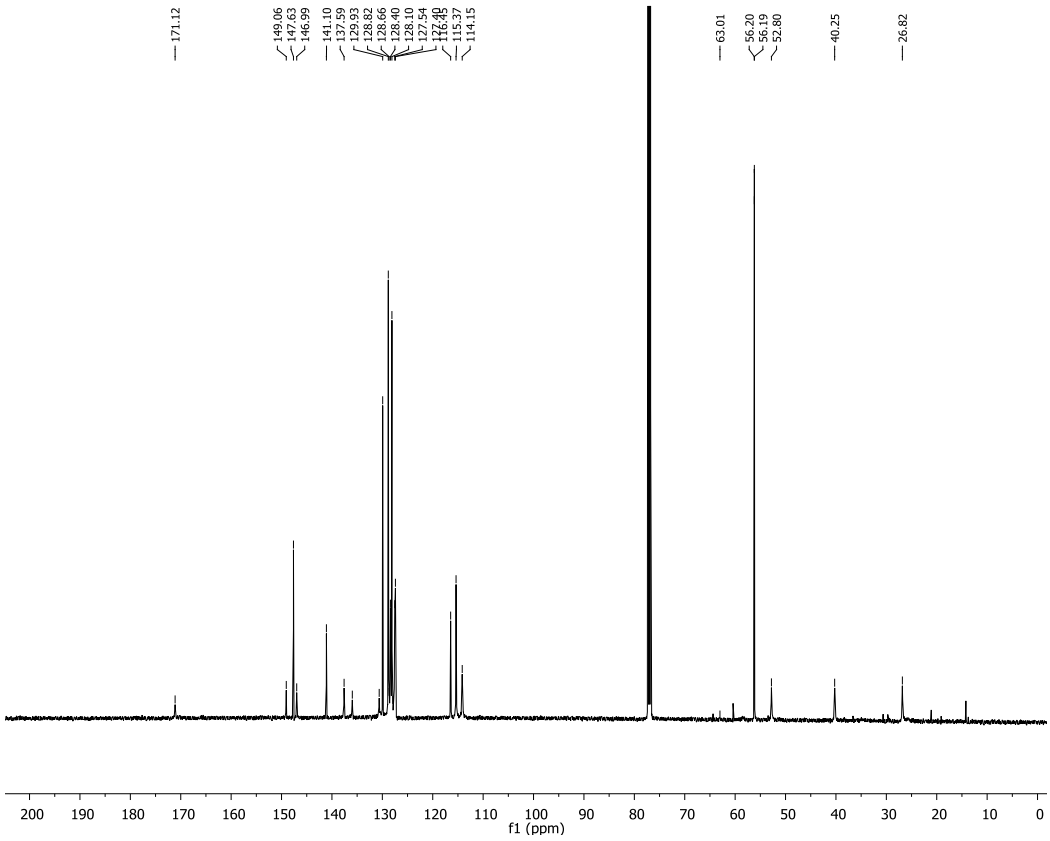

F
Br
N
N
O
Ph
4.12h
0.81
0.28
0.88
2.48
3.77
1.39
3.42
0.53
0.34
0.65
0.88
0.93
1.27
0.70
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

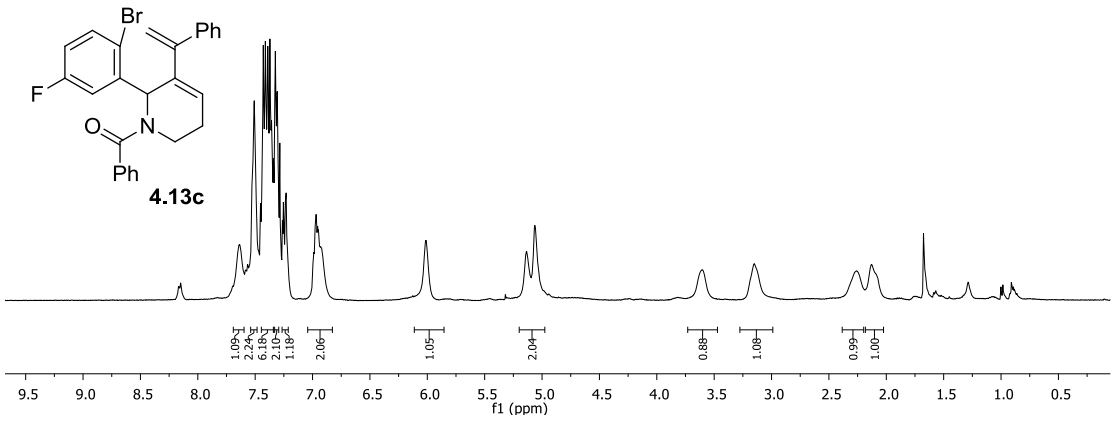

170.02
163.46
161.50
149.25
141.10
136.22
135.70
133.53
130.51
130.14
129.86
129.80
129.55
128.84
128.48
128.42
128.28
128.23
127.27
126.04
125.78
125.30
122.99
117.84
115.31
115.14
67.82
57.19
acetone
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

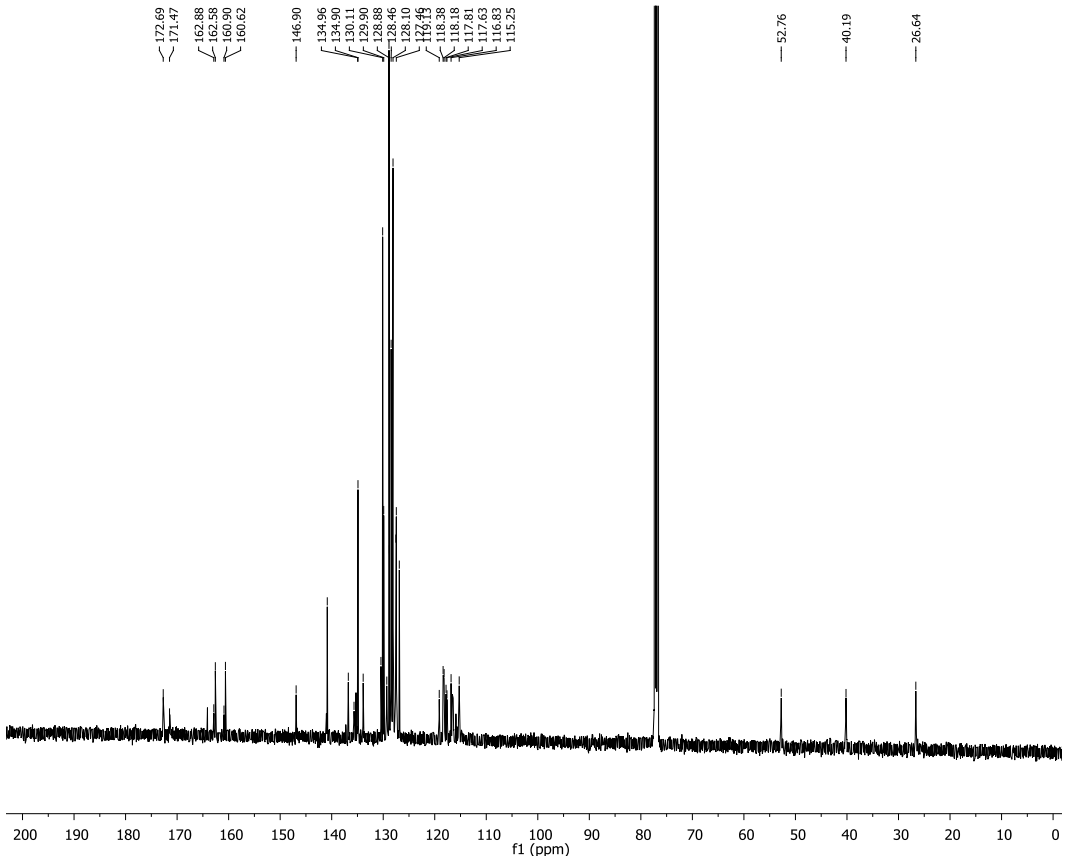

Br
Ph
O
N
Ph
4.13a
0.99
3.29
3.36
6.02
1.44
0.97
0.97
0.89
1.14
0.99
1.19
1.06
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

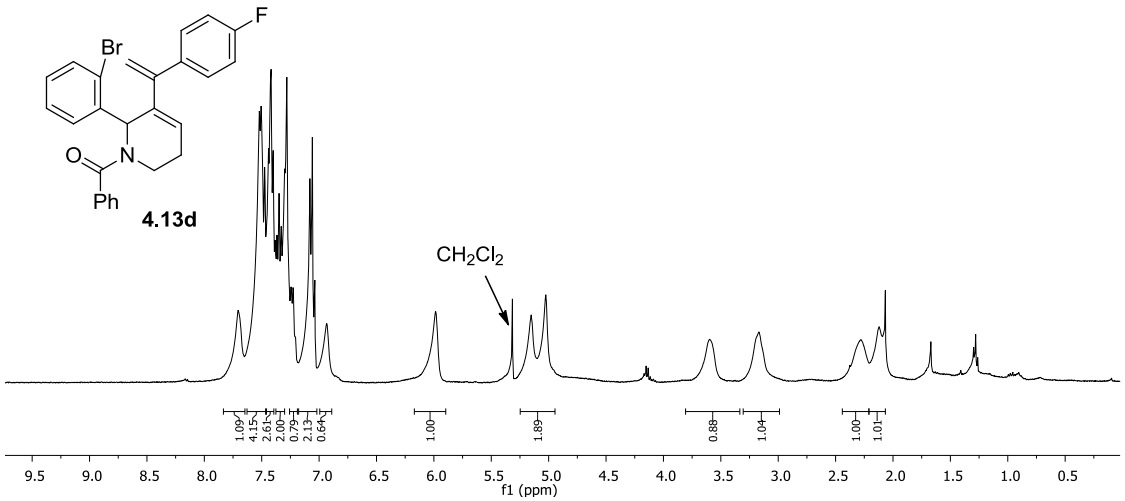

171.34
147.01
133.88
131.06
129.97
129.36
128.95
128.40
128.02
127.55
127.34
52.93
40.12
26.79
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

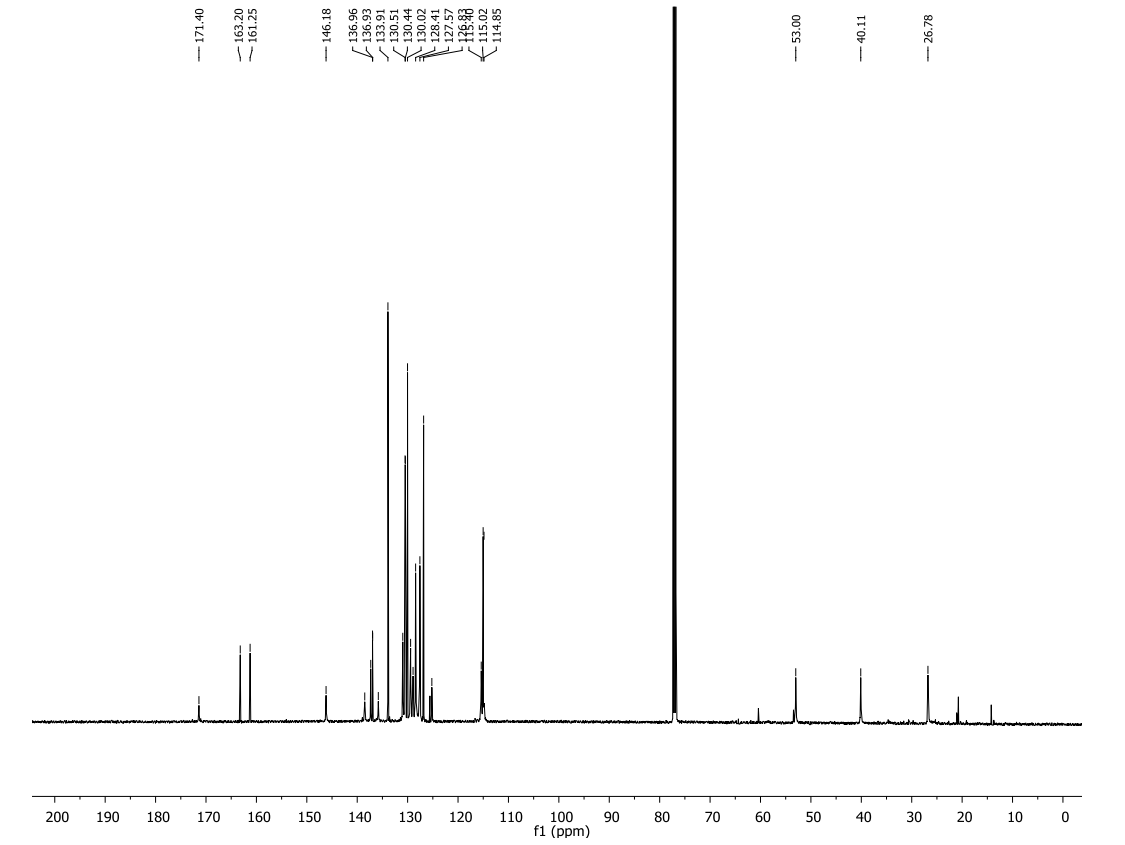

Br
Ph
O
O
O
N
Ph
4.13b
2.89
6.74
0.77
0.99
0.66
1.00
1.79
2.79
3.05
0.84
0.97
1.00
0.76
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

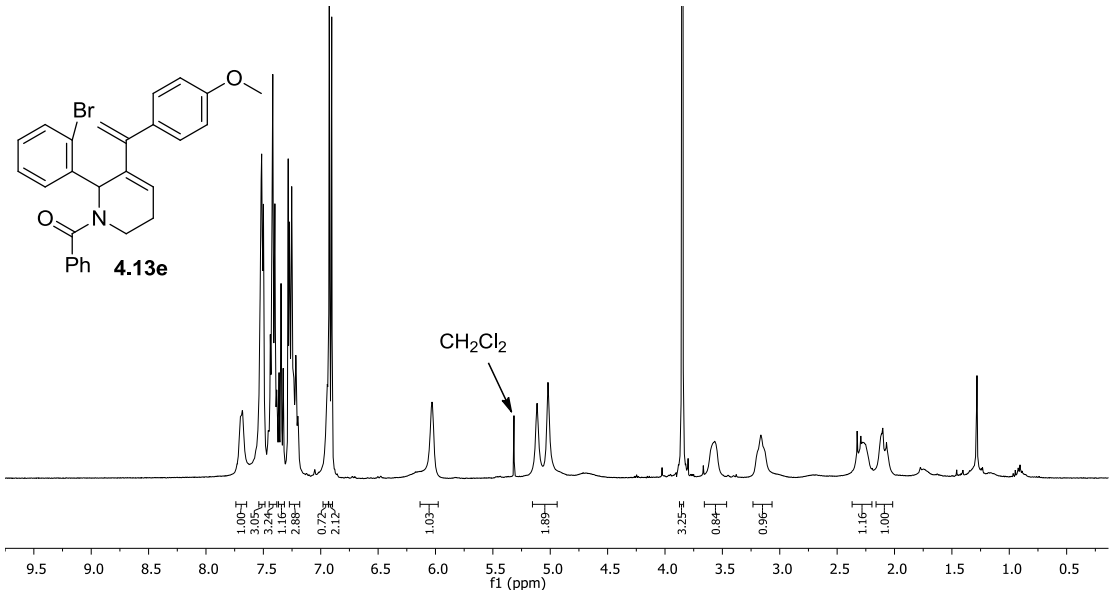

171.12
149.06
147.63
146.99
141.10
137.59
129.93
128.82
128.66
128.40
128.10
127.54
115.37
114.15
63.01
56.20
56.19
52.80
40.25
26.82
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

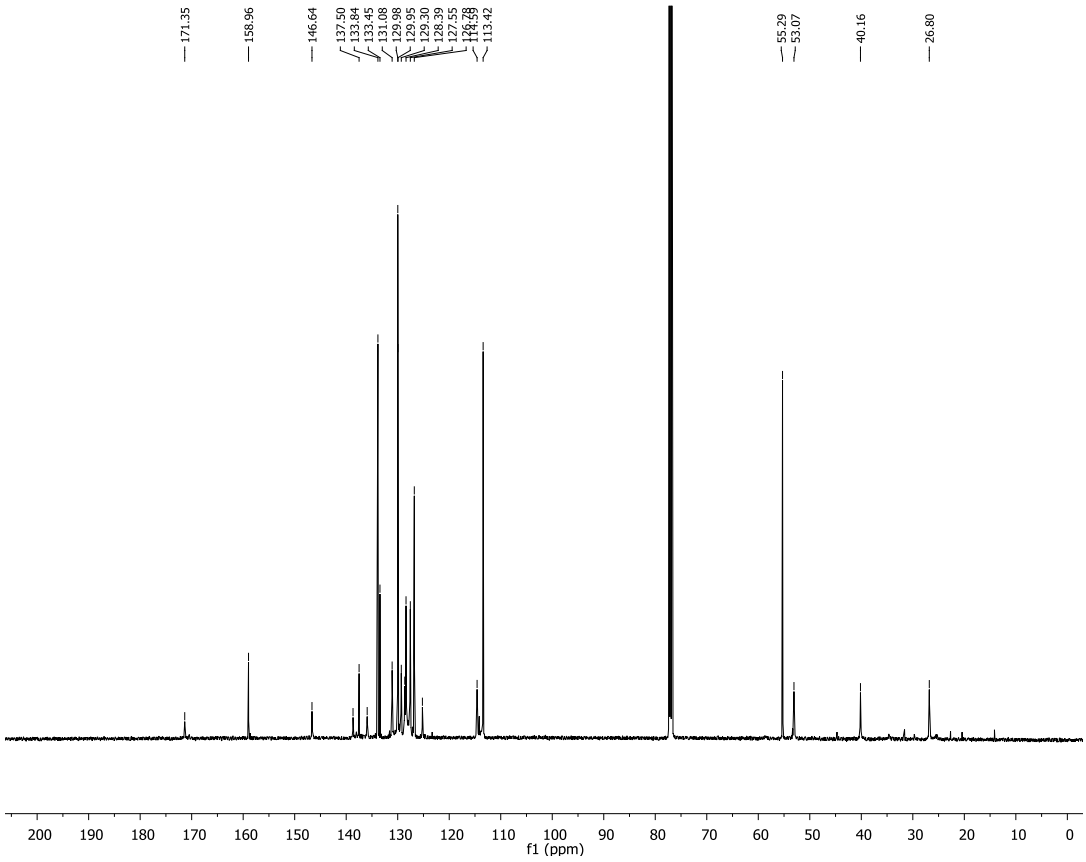

Br
Ph
F
O
N
Ph
4.13c
1.09
2.24
5.18
2.10
1.18
2.06
1.05
2.04
0.88
1.08
0.99
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

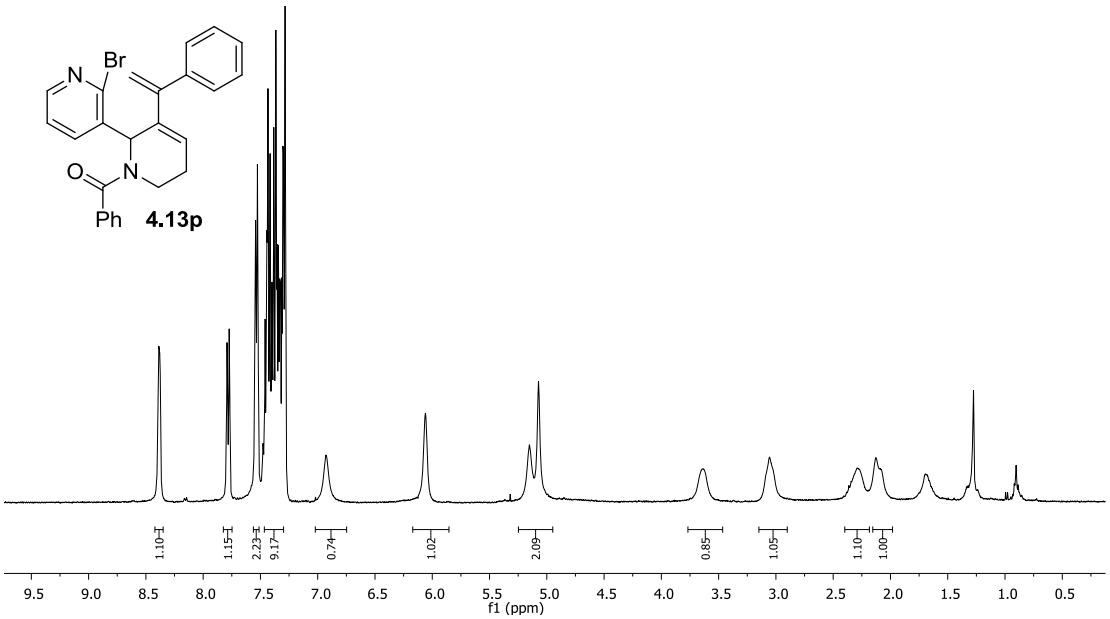

172.69
171.47
162.88
162.58
160.90
160.62
146.90
134.96
134.90
130.11
129.90
128.88
128.46
128.10
127.46
119.13
118.38
118.18
117.81
117.63
116.83
115.25
52.76
40.19
26.64
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

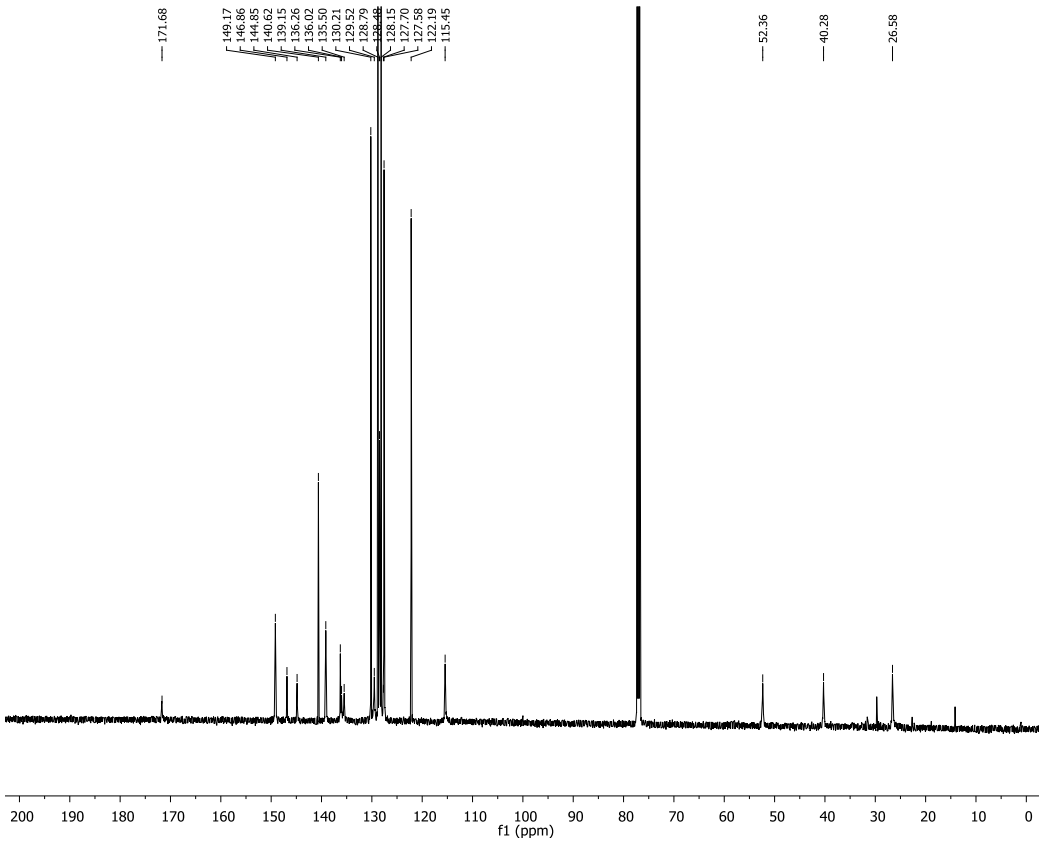

Br
F
O
N
Ph
4.13d
CH2Cl2
1.09
4.15
2.61
2.00
0.79
2.13
0.64
1.00
1.89
0.88
1.04
1.00
1.01
f1 (ppm)


171.40
163.20
161.25
146.18
136.96
136.93
133.91
130.51
130.44
130.02
128.41
127.57
115.02
114.85
53.00
40.11
26.78
f1 (ppm)


Br
O
O
N
Ph
4.13e
CH2Cl2
1.00
3.05
3.24
1.16
2.88
0.72
2.12
1.03
1.89
3.25
0.84
0.96
1.16
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


171.35
158.96
146.64
137.50
133.84
133.45
131.08
129.98
129.95
129.30
128.39
127.55
113.42
55.29
53.07
40.16
26.80
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
N
O
N
Ph
4.13p
1.10
1.15
2.23
9.17
0.74
1.02
2.09
0.85
1.05
1.10
1.00
f1 (ppm)


171.68
149.17
146.86
144.85
140.62
139.15
136.26
136.02
135.50
130.21
129.52
128.79
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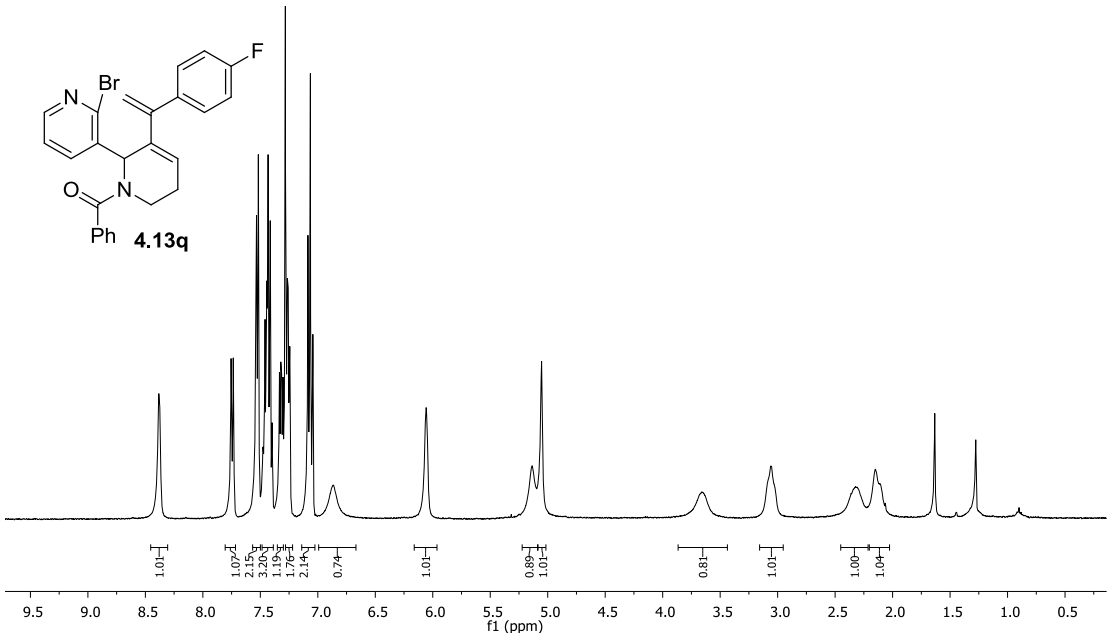
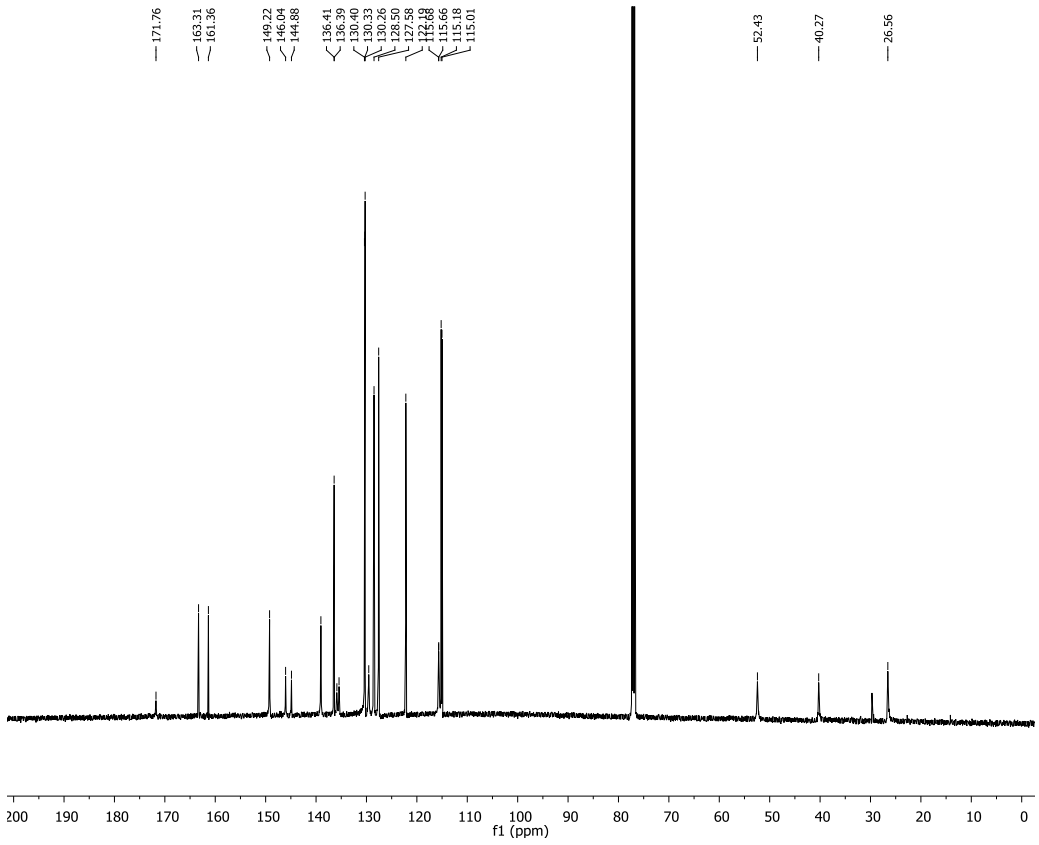
128.15
127.70
127.58
122.19
115.45
52.36
40.28
26.58
f1 (ppm)


F
Br
N
O
N
Ph
4.13q
1.01
1.07
2.15
3.20
1.95
1.76
2.14
0.74
1.01
0.89
1.01
0.81
1.01
1.00
1.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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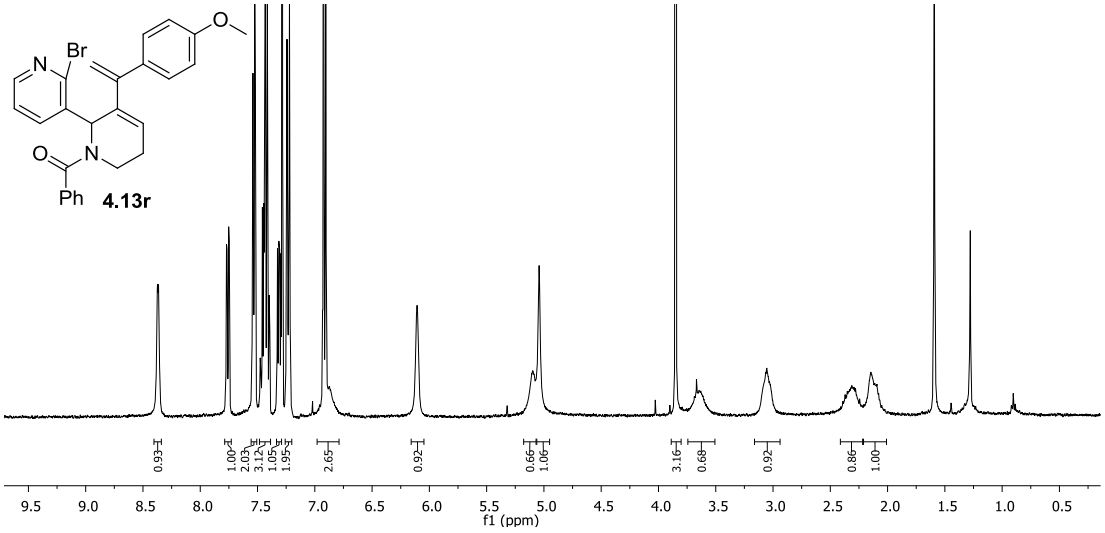
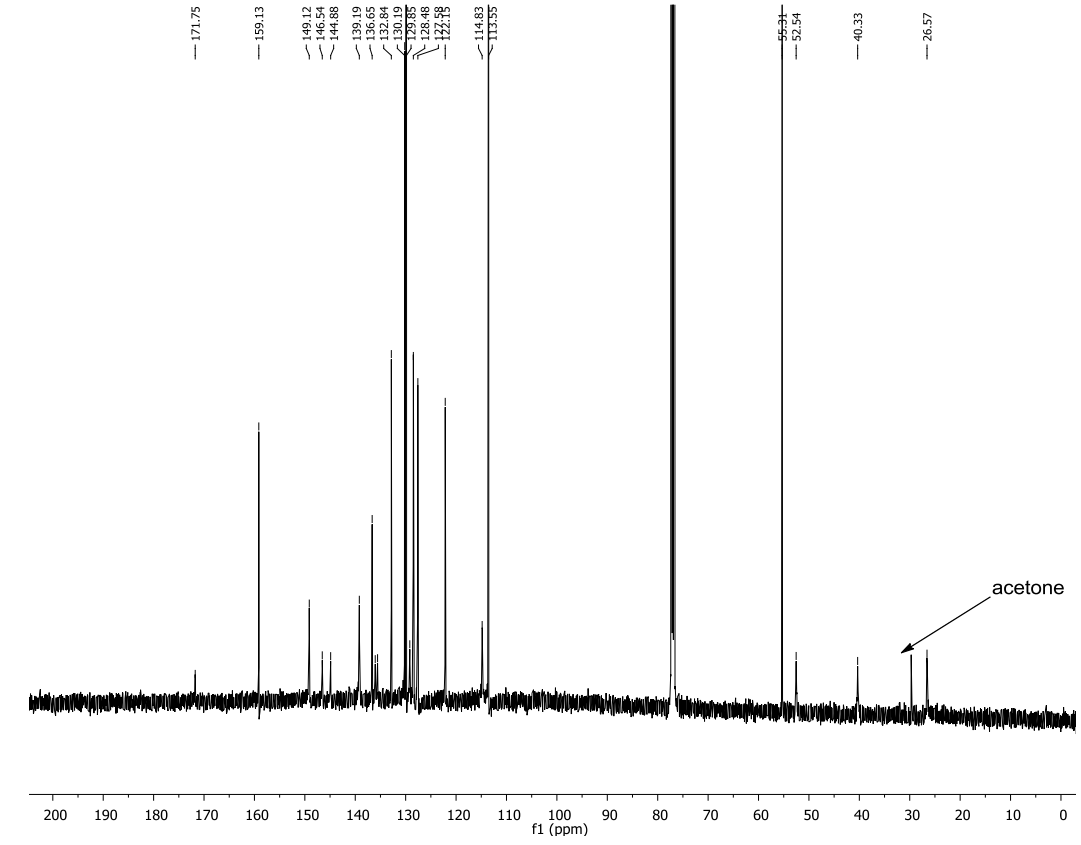
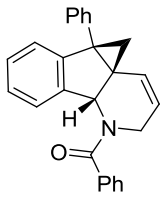
163.31
161.36
149.22
146.04
144.88
136.41
136.39
130.40
130.33
130.26
128.50
127.58
115.66
115.18
115.01
52.43
40.27
26.56
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

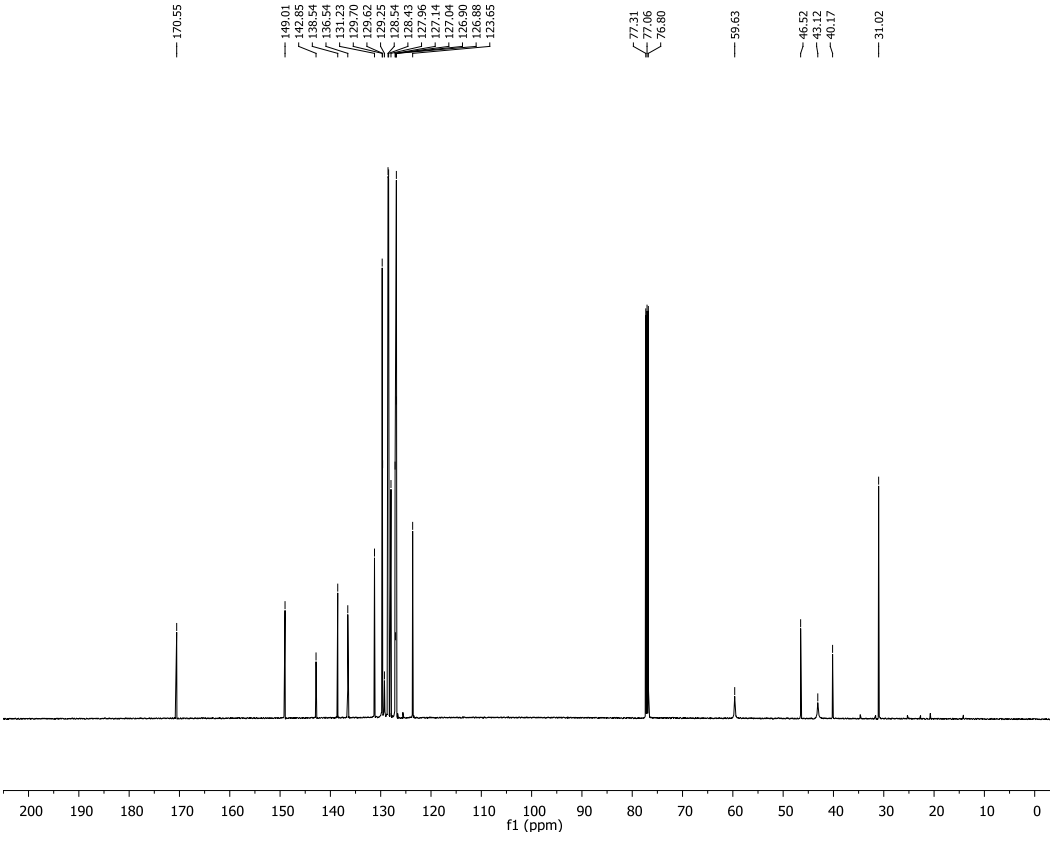

Br
N
O
O
N
Ph
4.13r
0.93
1.00
2.05
3.12
1.05
1.95
2.65
0.92
0.66
1.06
3.16
0.68
0.92
0.86
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

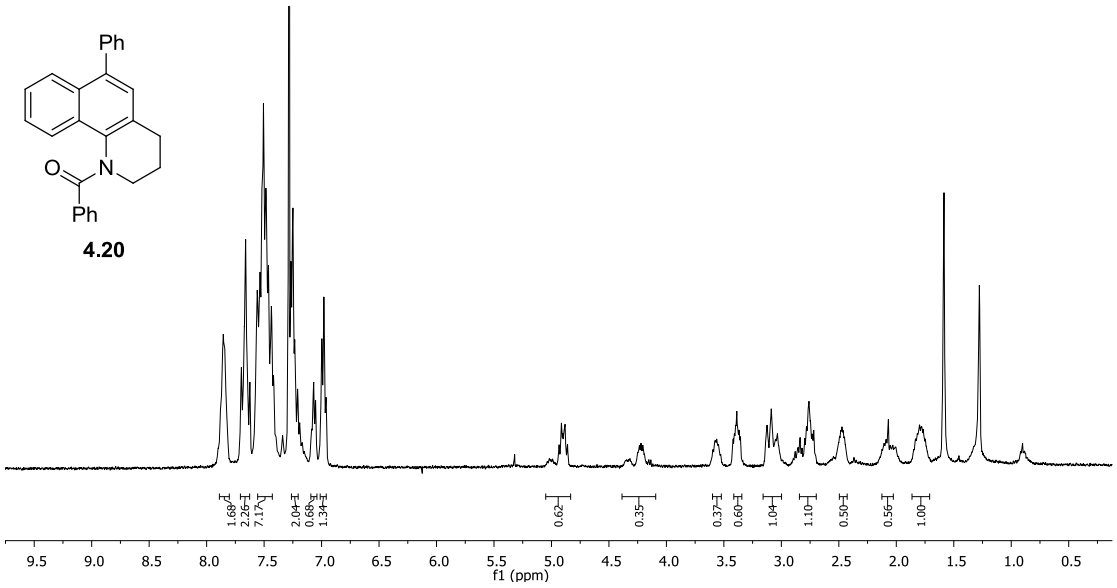

171.75
159.13
149.12
146.54
144.88
139.19
136.65
132.84
130.19
129.85
128.48
127.58
122.15
114.83
113.55
55.31
52.54
40.33
26.57
acetone
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

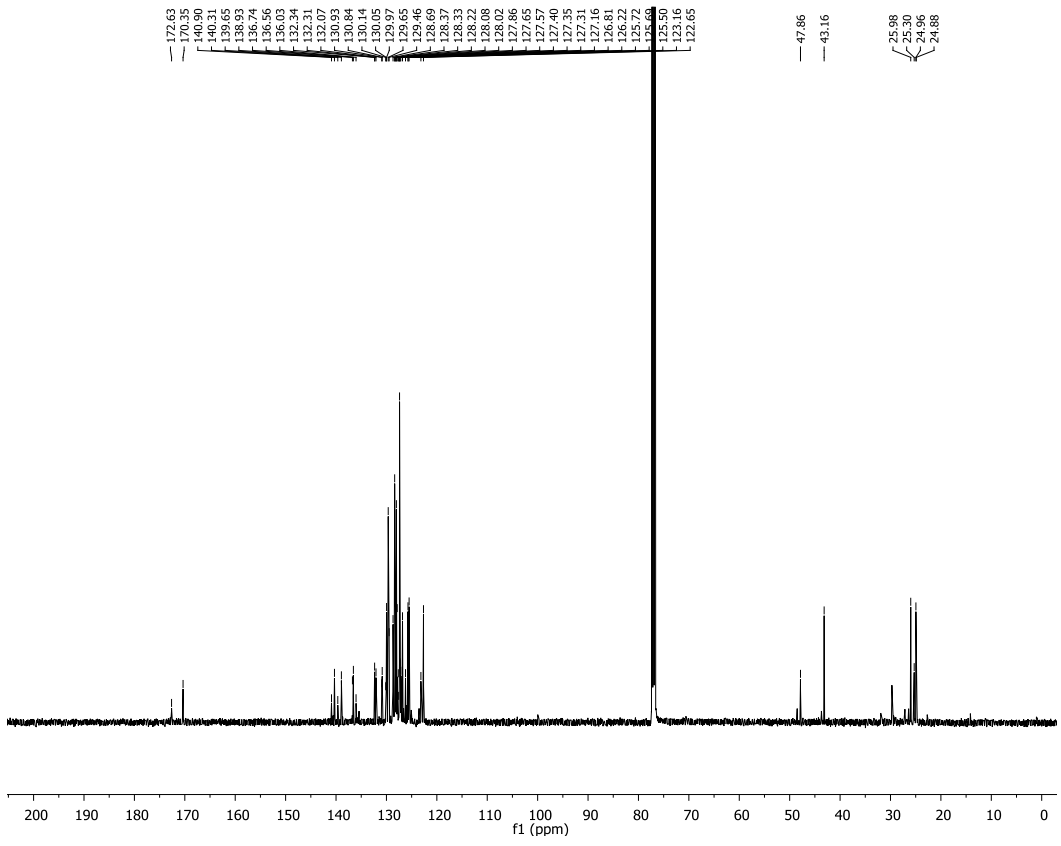

Ph
H
N
O
Ph

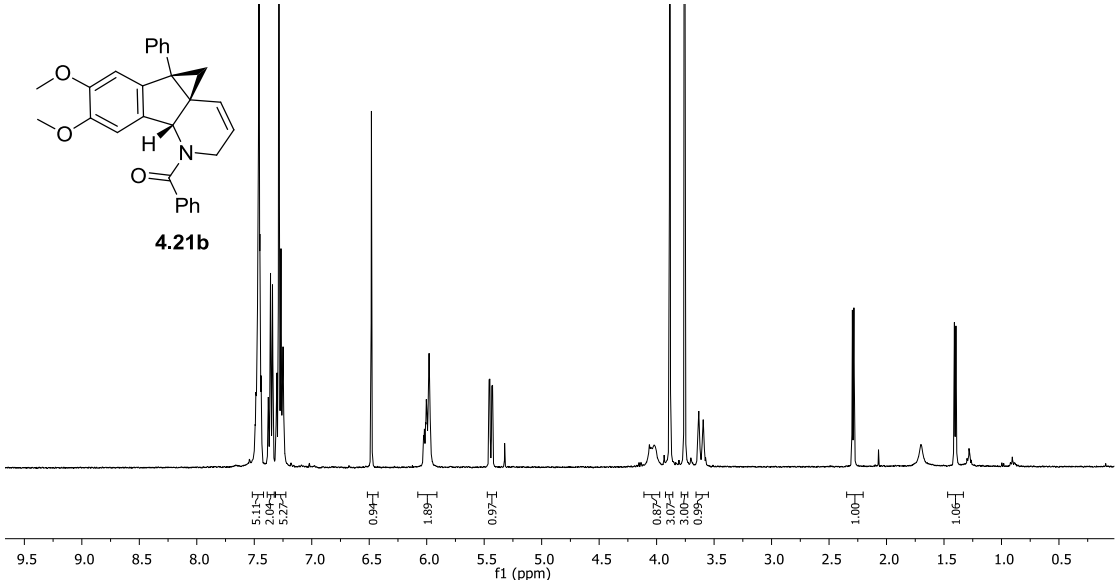
4.21a

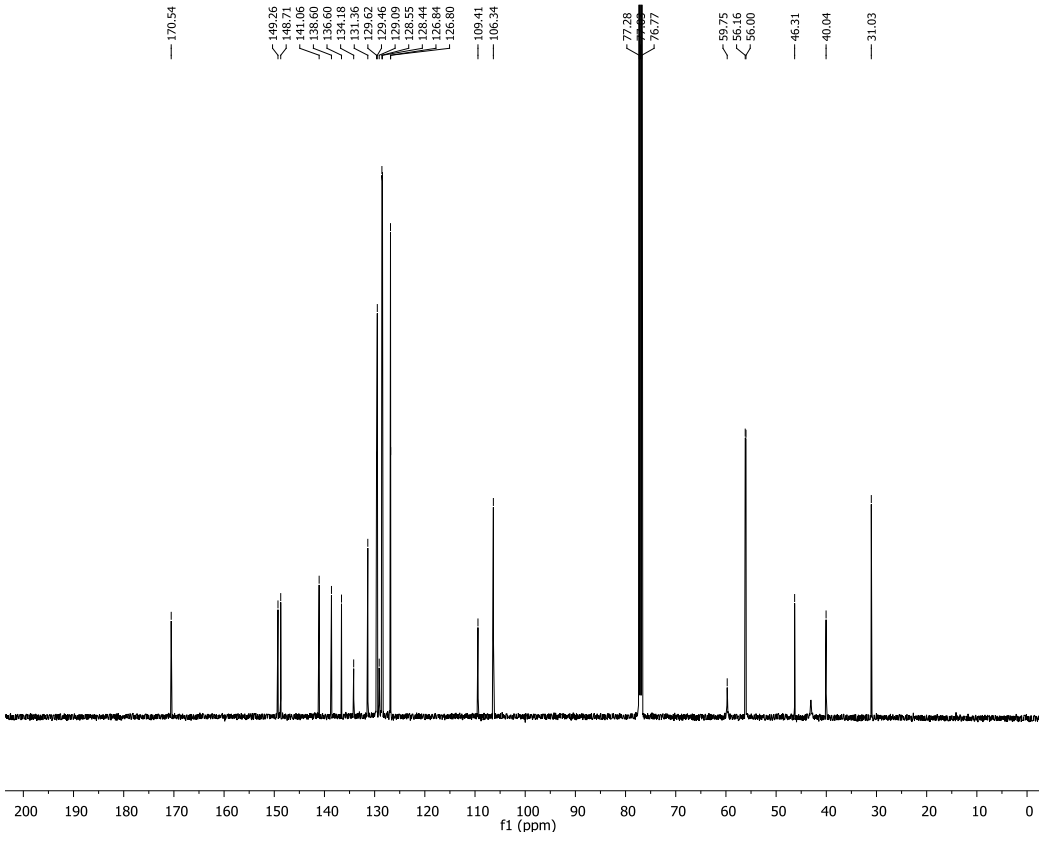
0.92
4.80
1.98
4.09
0.94
0.93
1.81
0.89
0.86
0.93
0.94
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

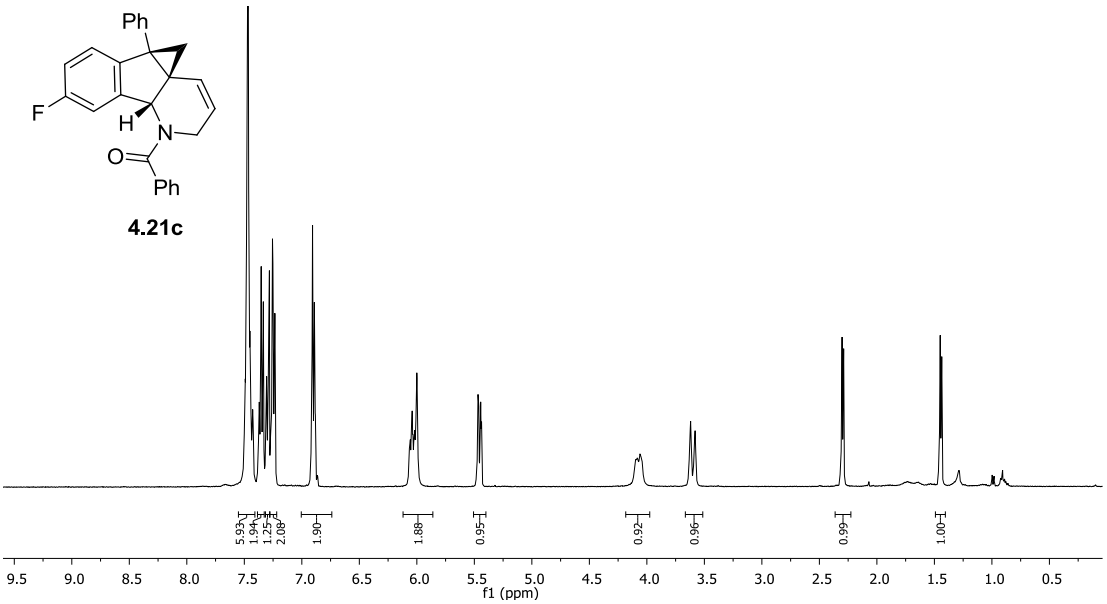

170.55
149.01
142.85
138.54
136.54
131.23
129.70
129.62
129.25
128.54
128.43
127.96
127.14
127.04
126.90
126.88
123.65
77.31
77.06
76.80
59.63
46.52
43.12
40.17
31.02
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

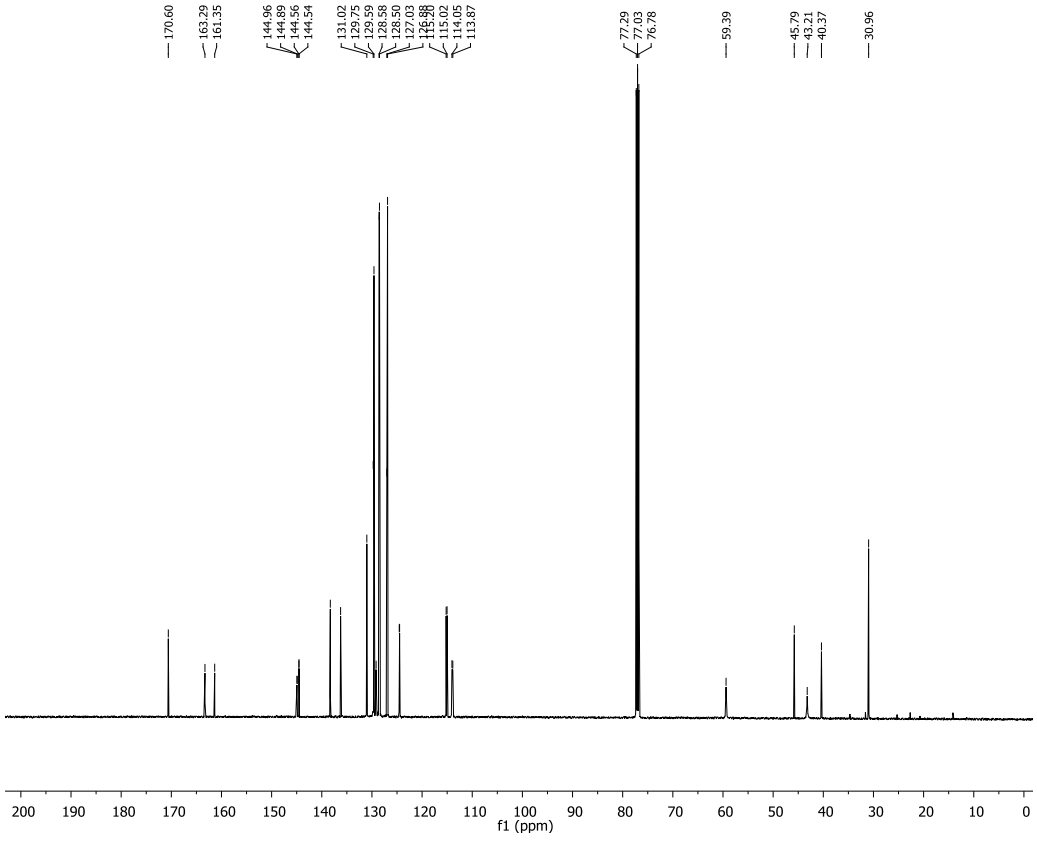

Ph
O
N
Ph
4.20
1.68
2.26
7.17
2.04
0.68
1.34
0.62
0.35
0.37
0.60
1.04
1.10
0.50
0.56
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

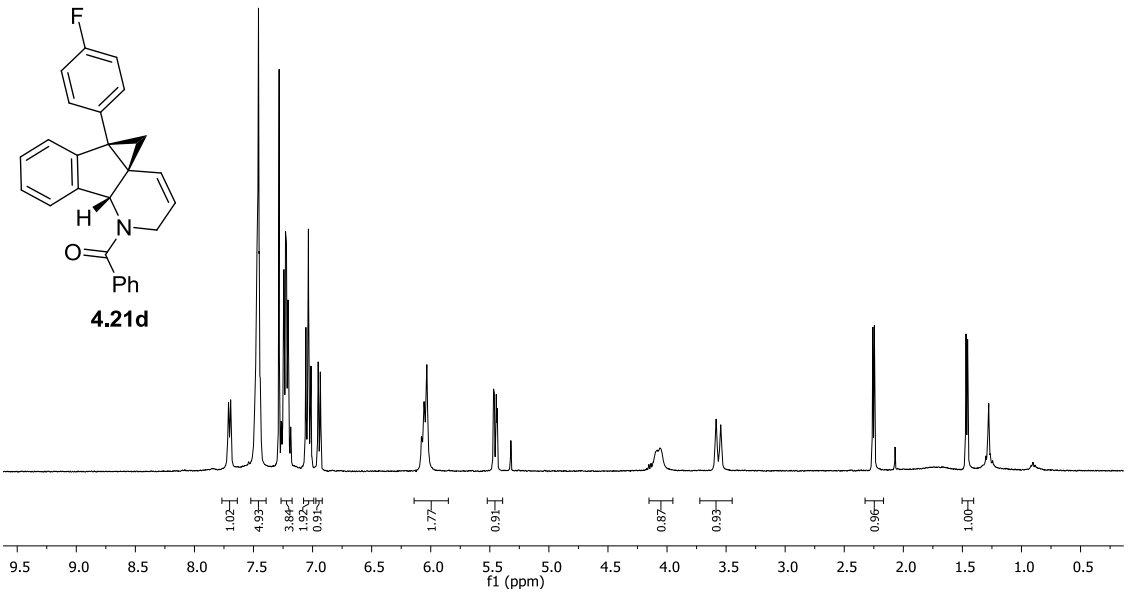

172.63
170.35
140.90
140.31
139.65
138.93
136.74
136.56
136.03
132.34
132.21
132.07
130.93
130.84
130.14
130.05
129.97
129.65
129.46
128.69
128.37
128.33
128.22
128.08
128.02
127.86
127.65
127.57
127.40
127.35
127.31
127.16
126.81
126.22
125.72
125.69
125.50
123.16
122.65
47.86
43.16
25.98
25.30
24.96
24.88
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

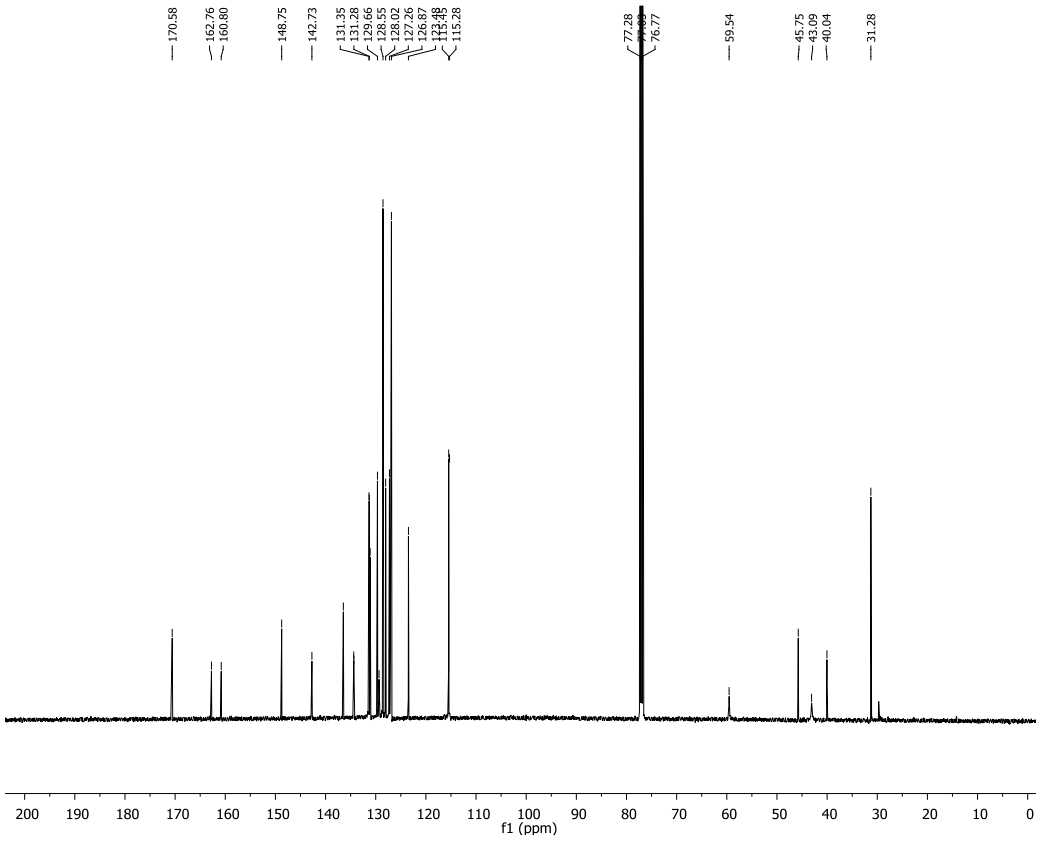

Ph
O
O
H
N
O
Ph
4.21b
5.11
2.04
5.27
0.94
1.89
0.97
0.87
3.07
3.00
0.99
1.00
1.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

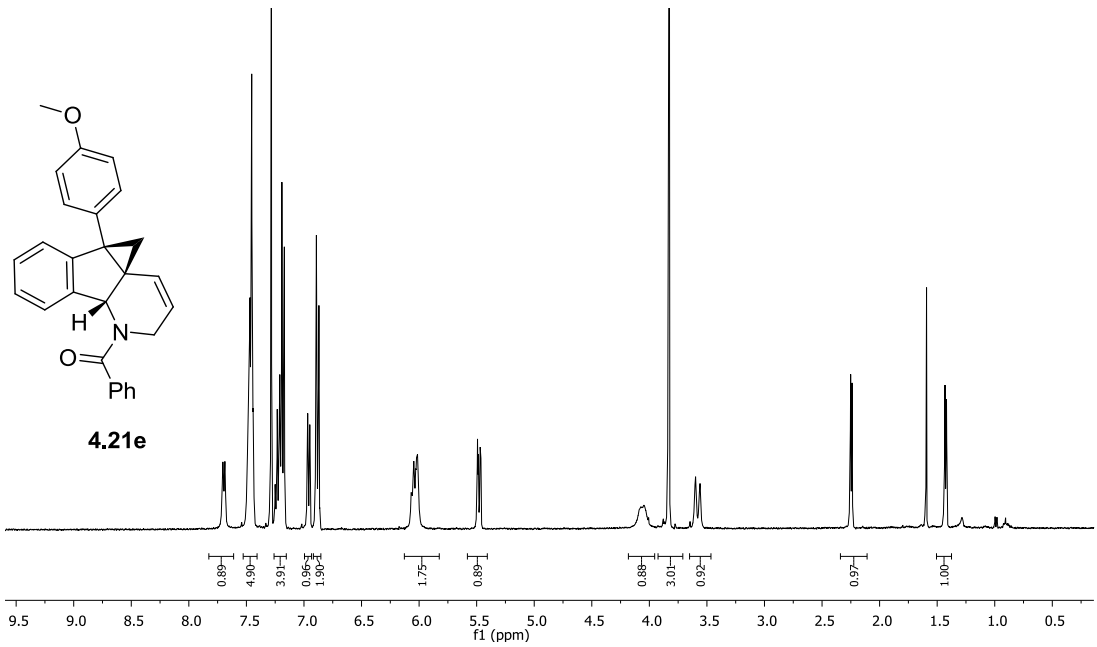

170.54
149.26
148.71
141.06
138.60
136.60
134.18
131.36
129.62
129.46
129.09
128.55
128.44
126.84
126.80
109.41
106.34
77.28
77.03
76.77
59.75
56.16
56.00
46.31
40.04
31.03
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

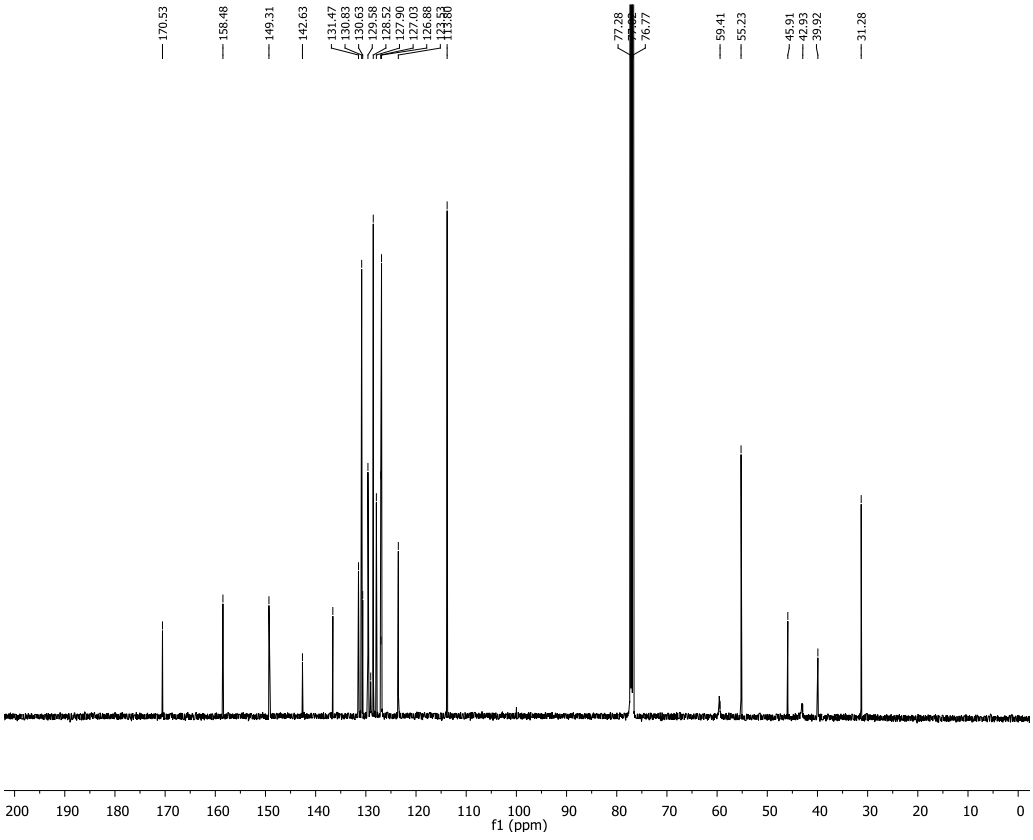

Ph
F
H
N
O
Ph
4.21c
5.93
1.94
1.25
2.08
1.90
1.88
0.95
0.92
0.96
0.99
1.00
f1 (ppm)

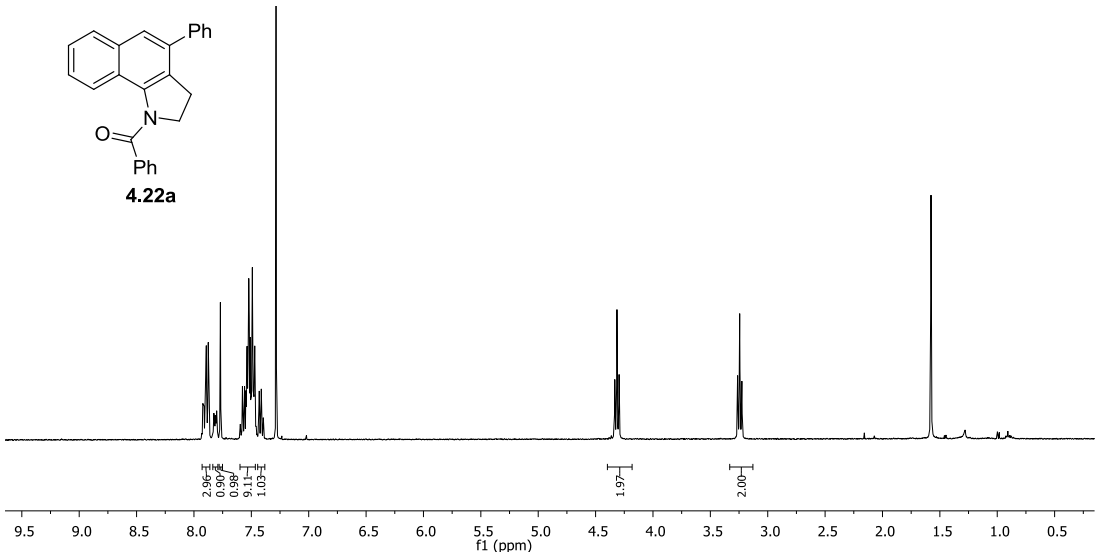

170.60
163.29
161.35
144.96
144.89
144.56
144.54
131.02
129.75
129.59
128.58
128.50
127.03
115.02
114.05
113.87
77.29
77.03
76.78
59.39
45.79
43.21
40.37
30.96
f1 (ppm)

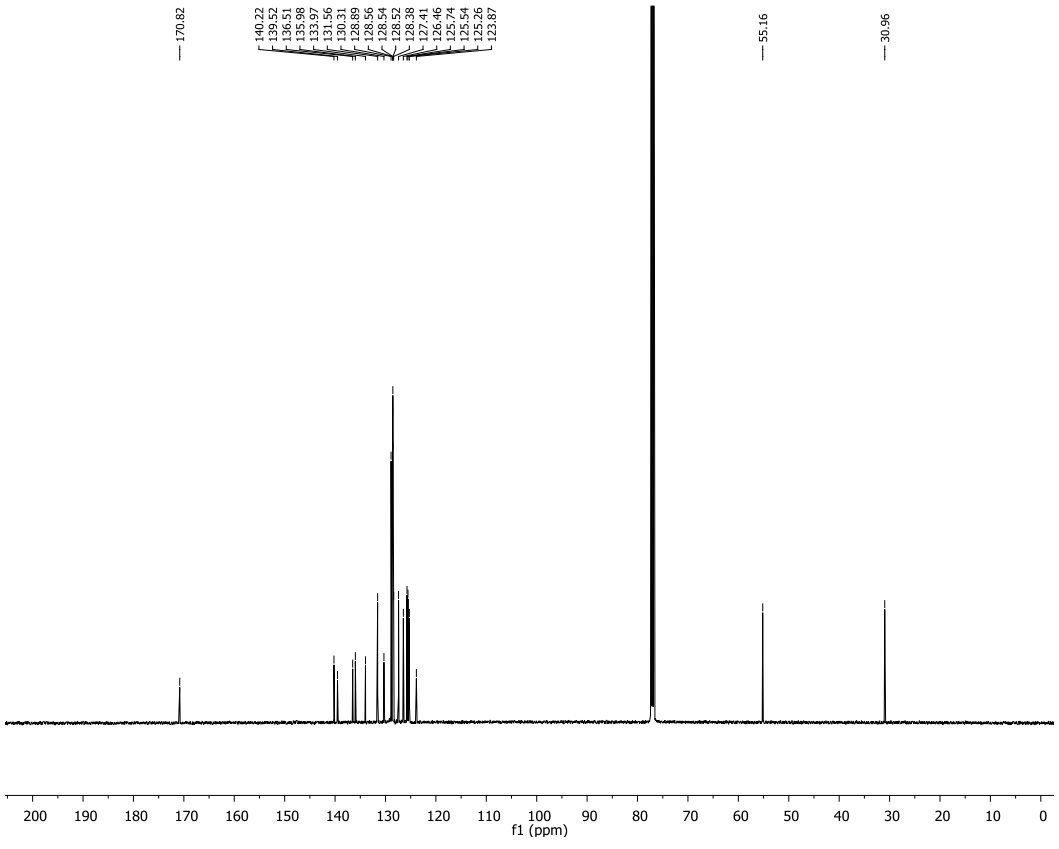

F
H
N
O
Ph
4.21d
1.02
4.93
3.84
1.92
0.91
1.77
0.91
0.87
0.93
0.96
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

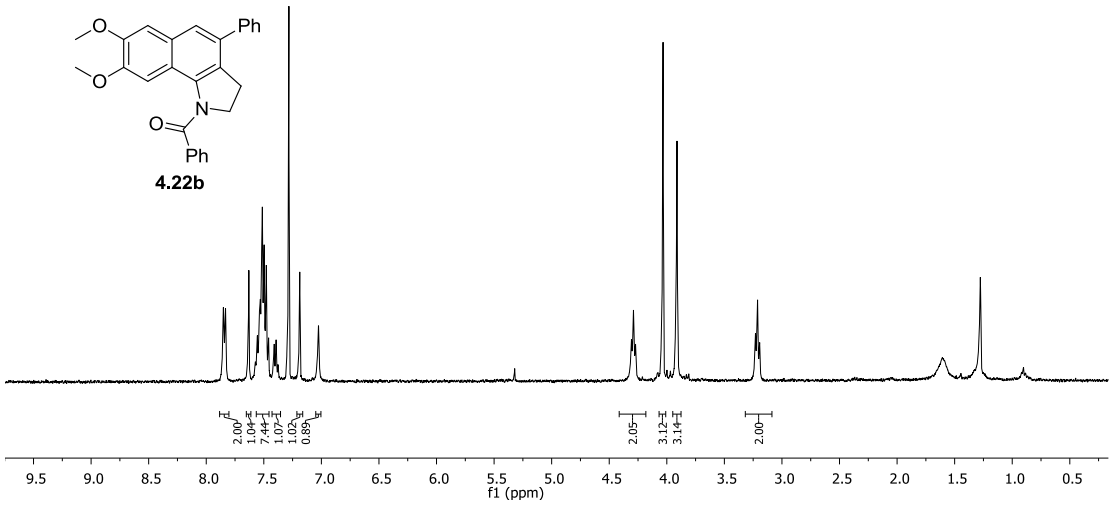

170.58
162.76
160.80
148.75
142.73
131.35
131.28
129.66
128.55
128.02
127.56
126.87
123.48
115.40
115.28
77.28
77.03
76.77
59.54
45.75
43.09
40.04
31.28
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

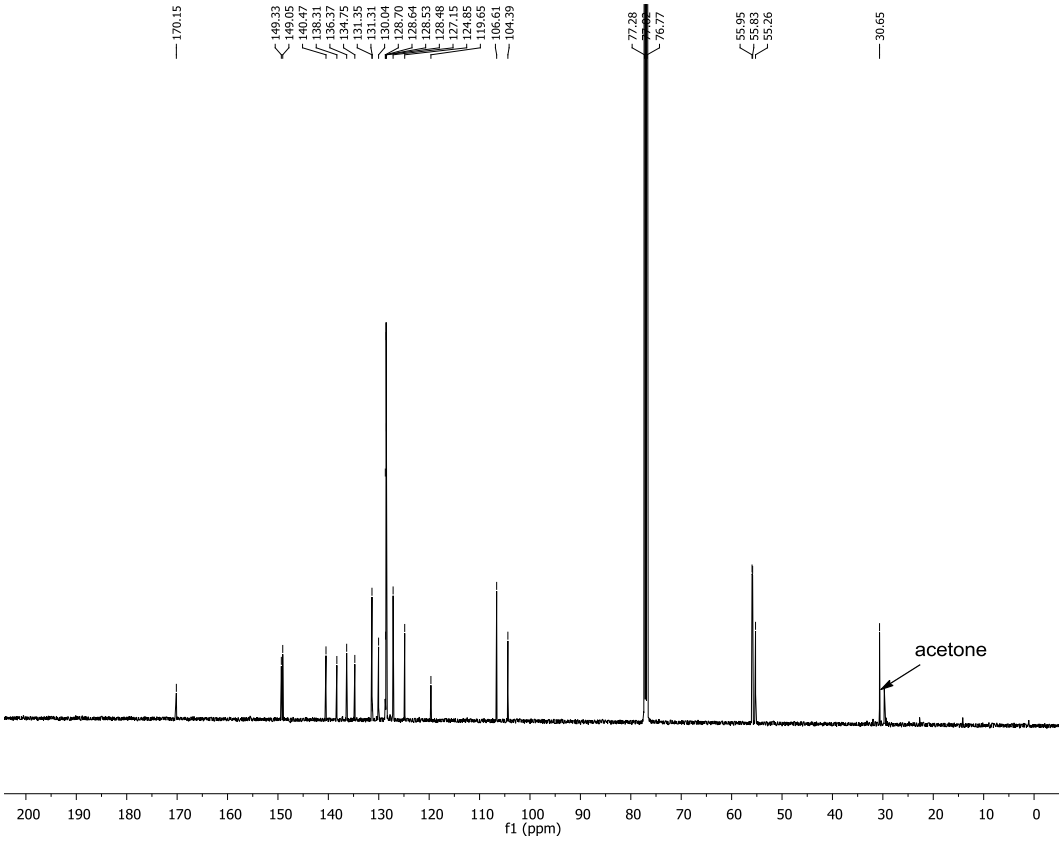

O
H
N
O
Ph
4.21e
0.89
4.90
3.91
0.96
1.90
1.75
0.89
0.88
3.01
0.92
0.97
1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

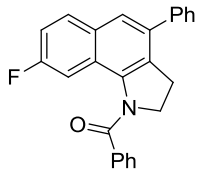

170.53
158.48
149.31
142.63
131.47
130.83
130.63
129.58
128.52
127.90
127.03
126.88
113.80
77.28
76.77
59.41
55.23
45.91
42.93
39.92
31.28
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
N
O
Ph
4.22a
2.96
0.90
0.98
9.11
1.03
1.97
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

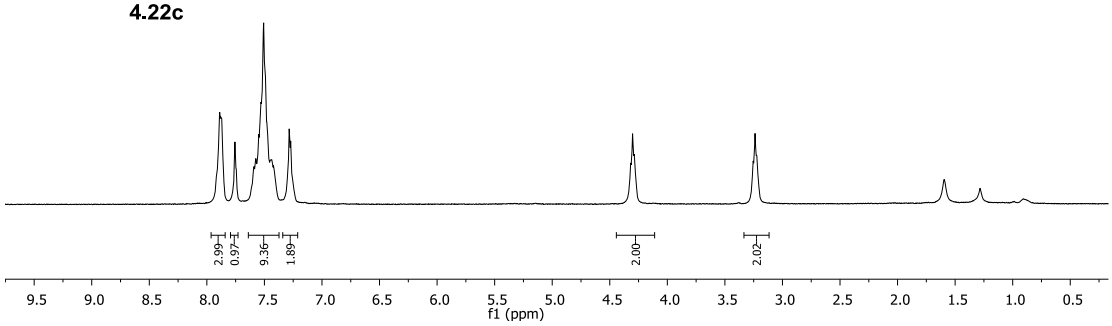

170.82
140.22
139.52
136.51
135.98
133.97
131.56
130.31
128.89
128.56
128.54
128.52
128.38
127.41
126.46
125.74
125.54
125.26
123.87
55.16
30.96
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

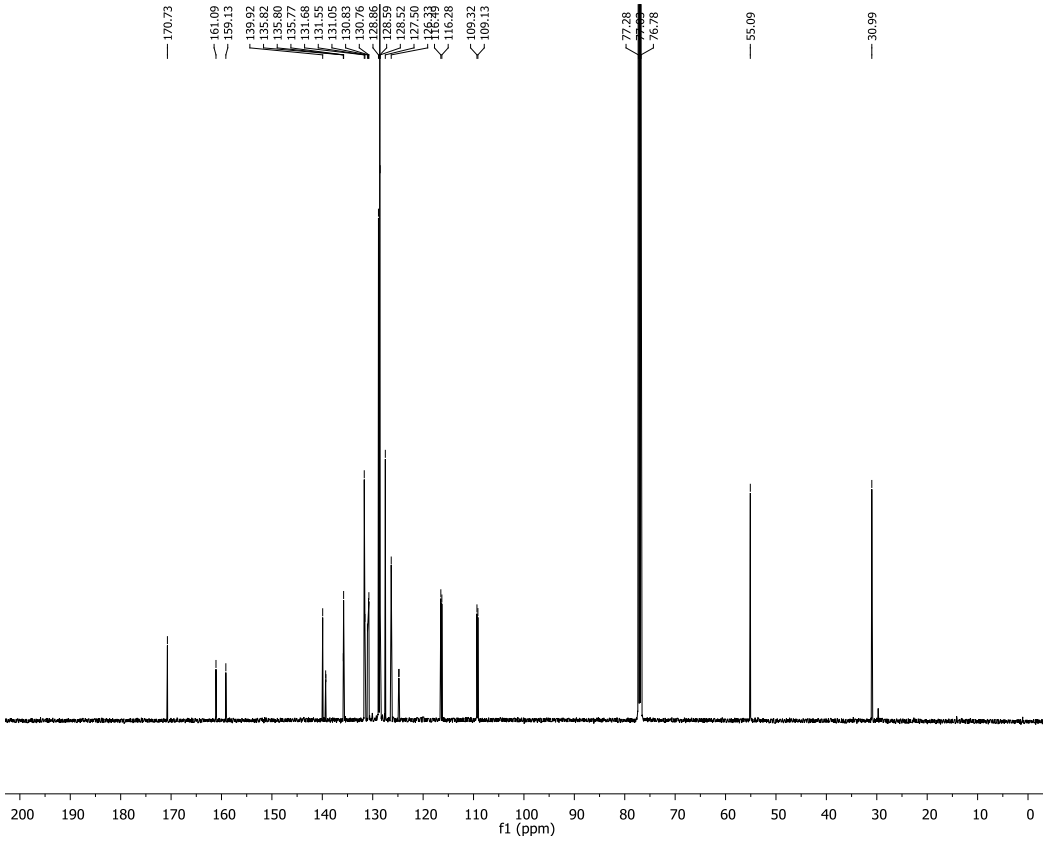

O
O
Ph
N
O
Ph
4.22b
2.00
1.04
7.44
1.07
1.02
0.89
2.05
3.12
3.14
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

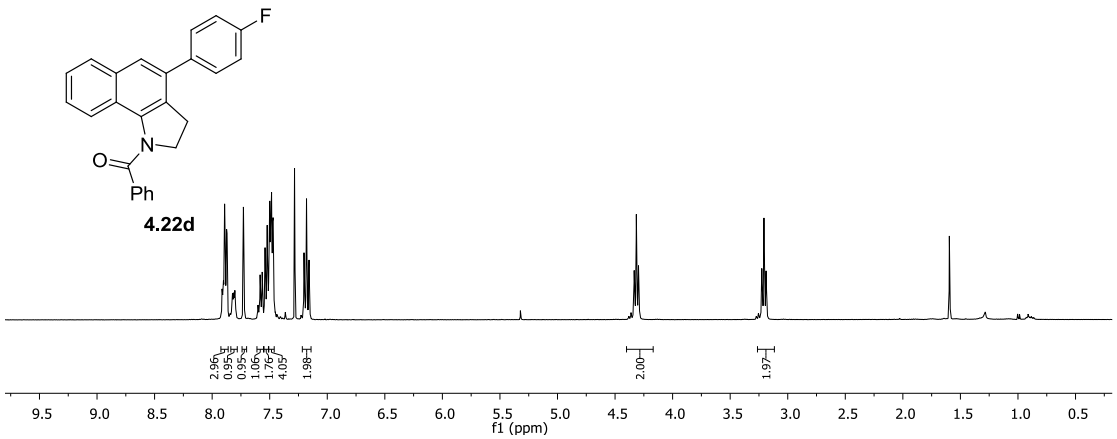

170.15
149.33
149.05
140.47
138.31
136.37
134.75
131.35
131.31
130.04
128.70
128.64
128.53
128.48
127.15
124.85
119.65
106.61
104.39
77.28
77.02
76.77
55.95
55.83
55.26
30.65
acetone
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

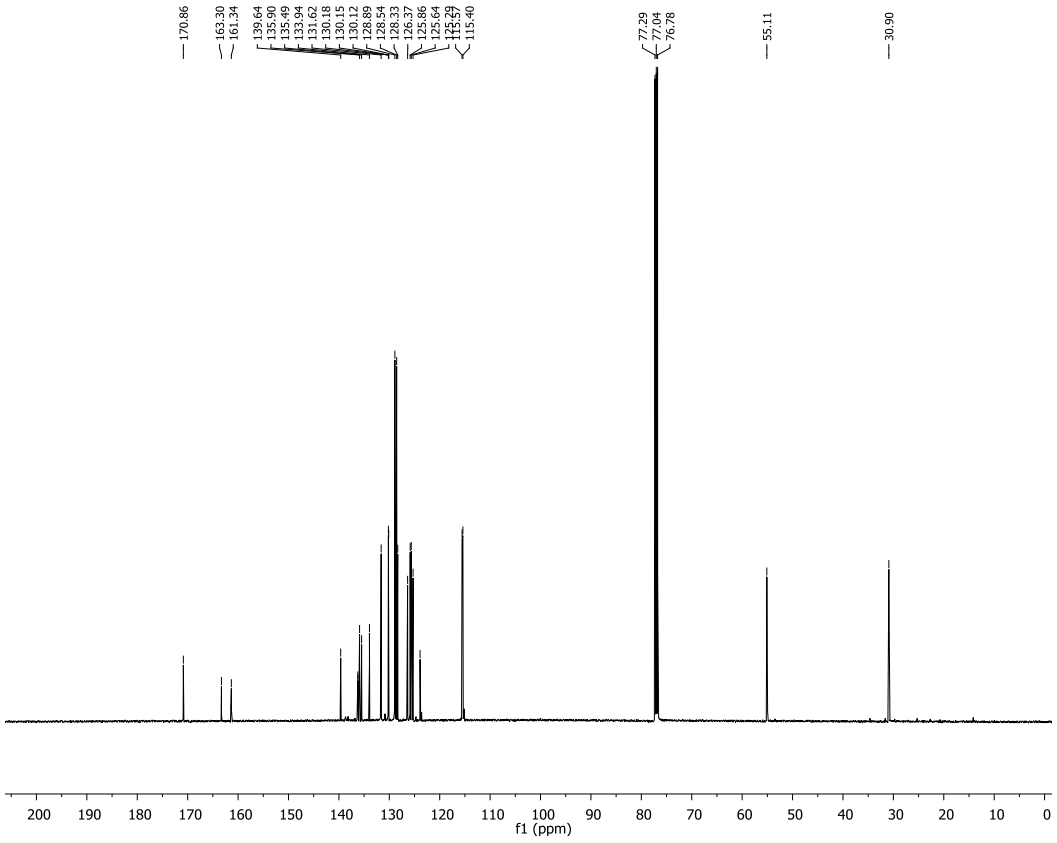

Ph
F
N
O
Ph

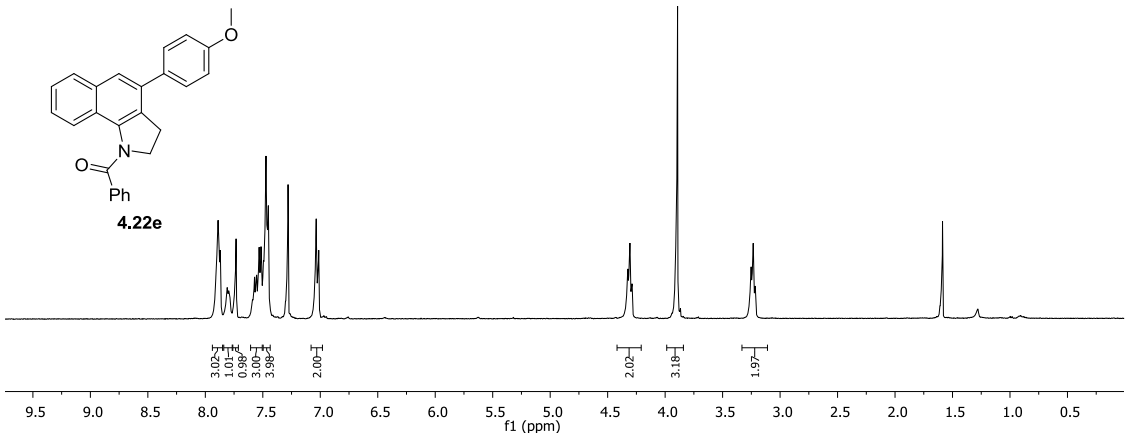
4.22c

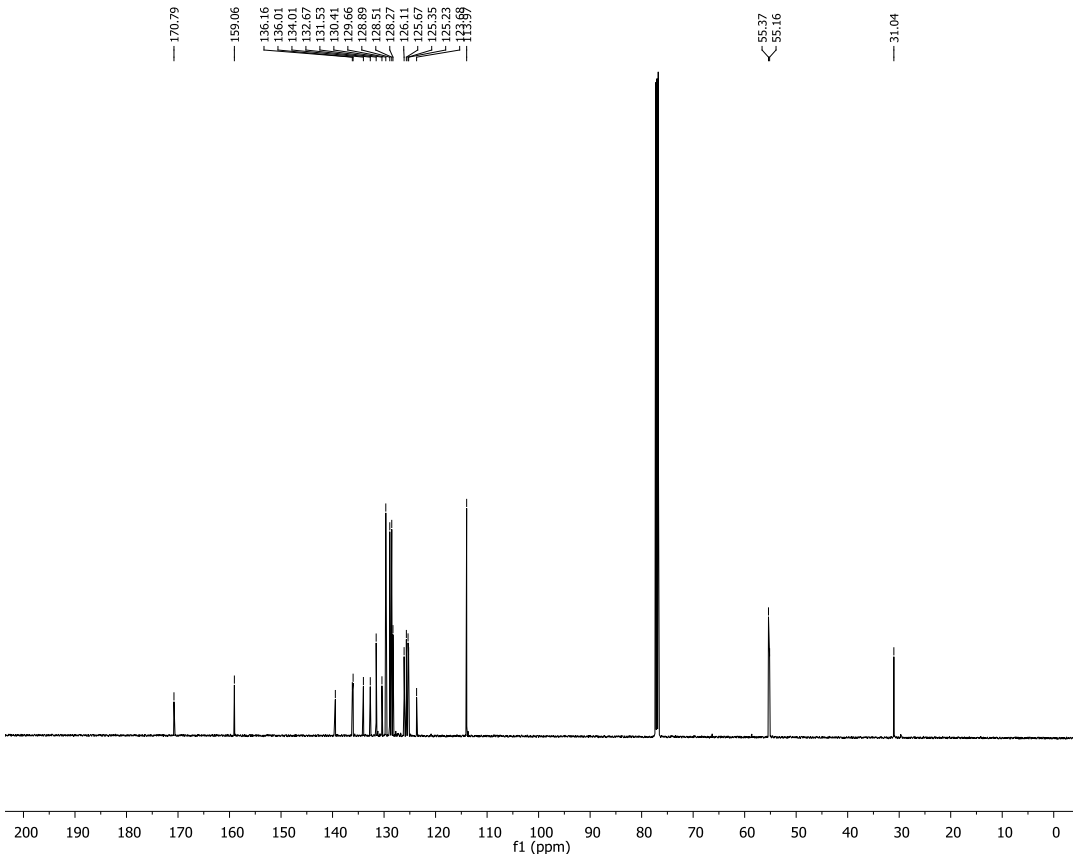

2.99
0.97
9.36
1.89
2.00
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

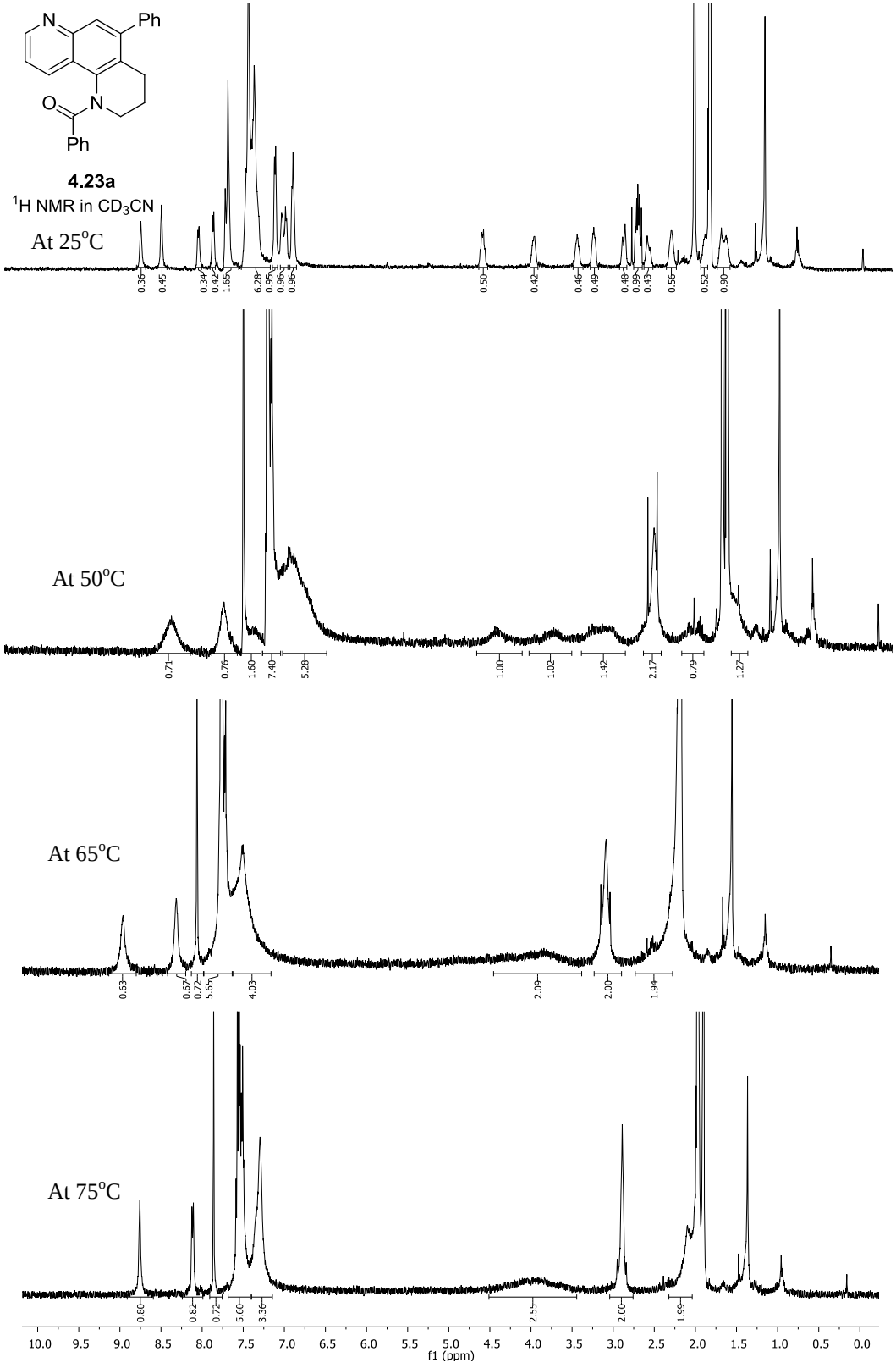

170.73
161.09
159.13
139.92
135.82
135.80
135.77
131.68
131.55
131.05
130.83
130.76
128.86
128.59
128.52
127.50
116.43
116.28
109.32
109.13
77.28
76.78
55.09
30.99
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

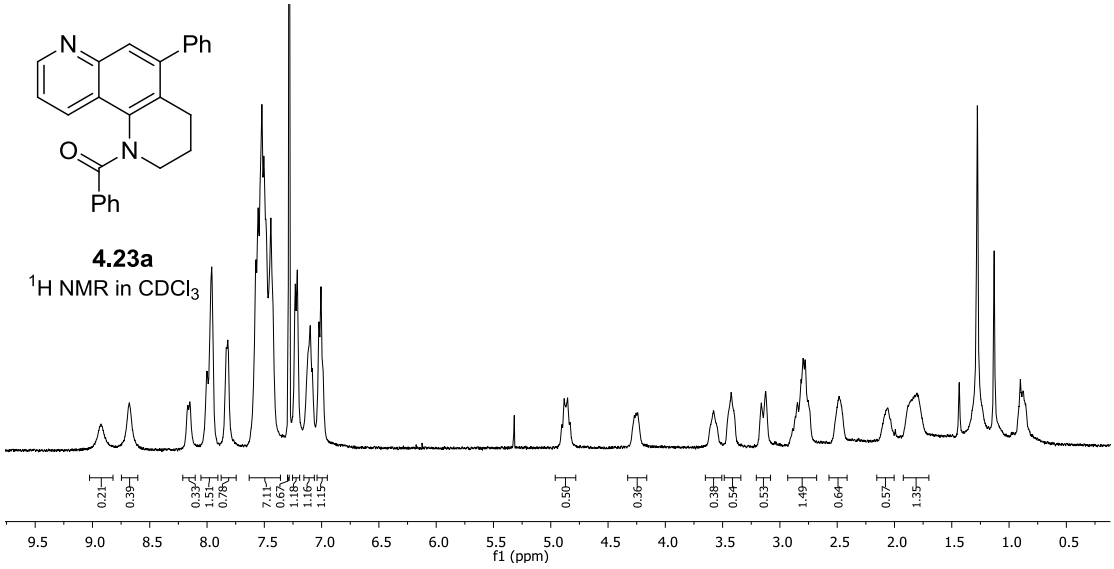

F
N
O
Ph
4.22d
2.96
0.95
0.95
1.06
1.76
4.05
1.98
2.00
1.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

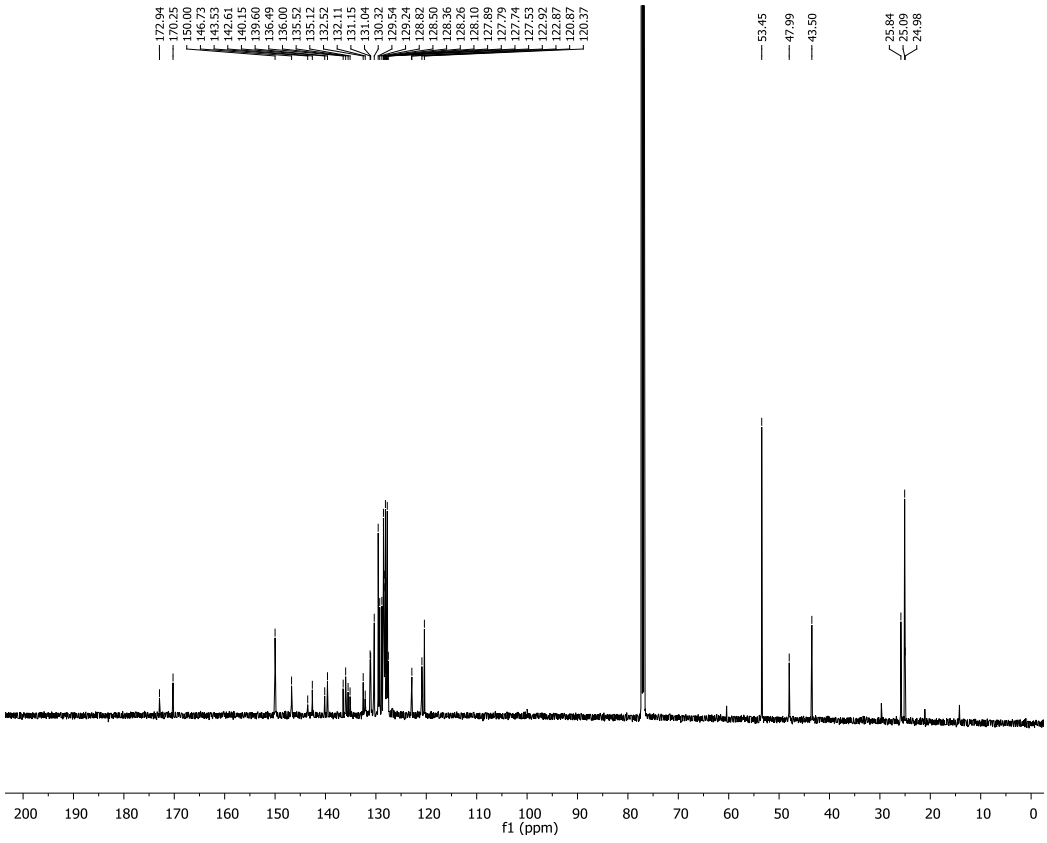

170.86
163.30
161.34
139.64
135.90
135.49
133.94
131.62
130.18
130.15
130.12
128.89
128.54
128.33
126.37
125.86
125.64
115.57
115.40
77.29
77.04
76.78
55.11
30.90
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

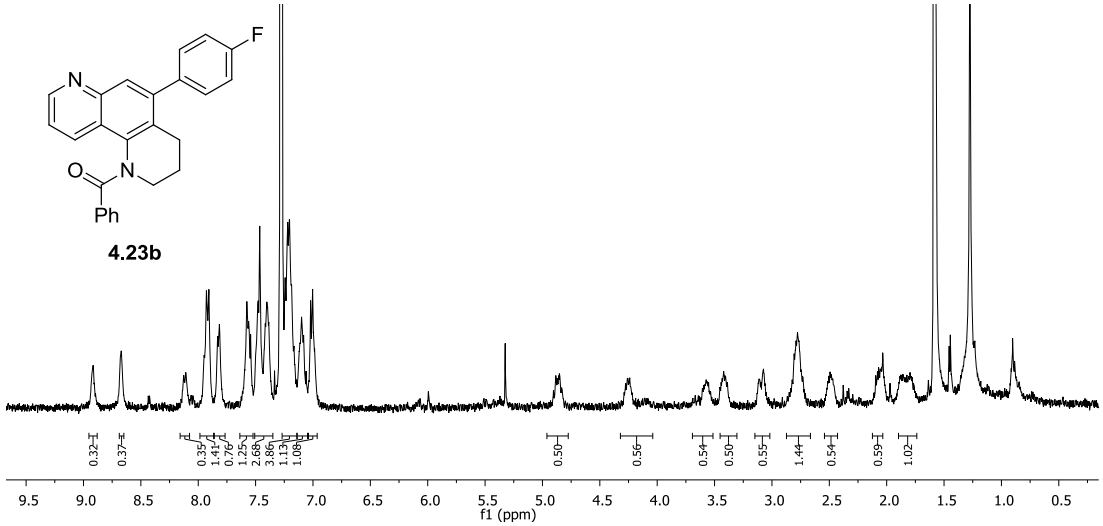

O
N
O
Ph
4.22e
3.02
1.01
0.98
3.00
3.99
2.00
2.02
3.18
1.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

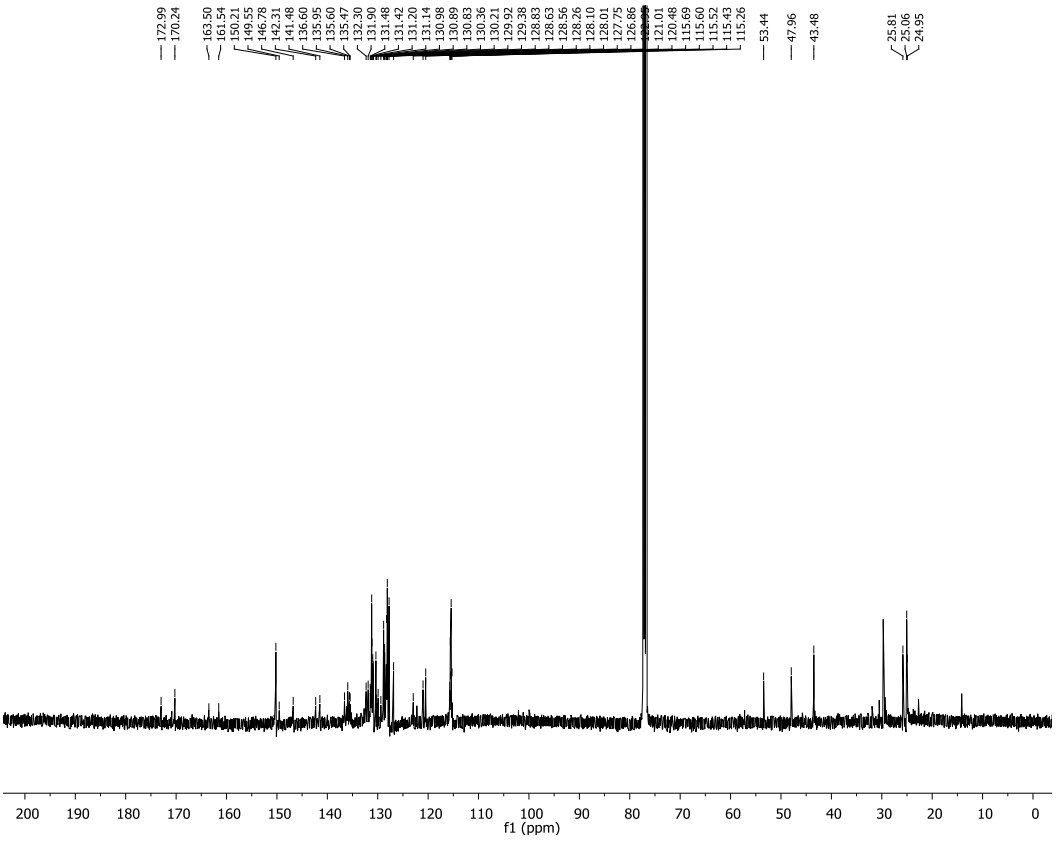

170.79
159.06
136.16
136.01
134.01
132.67
131.53
130.41
129.66
128.89
128.51
128.27
126.11
125.67
125.35
125.23
113.97
55.37
55.16
31.04
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

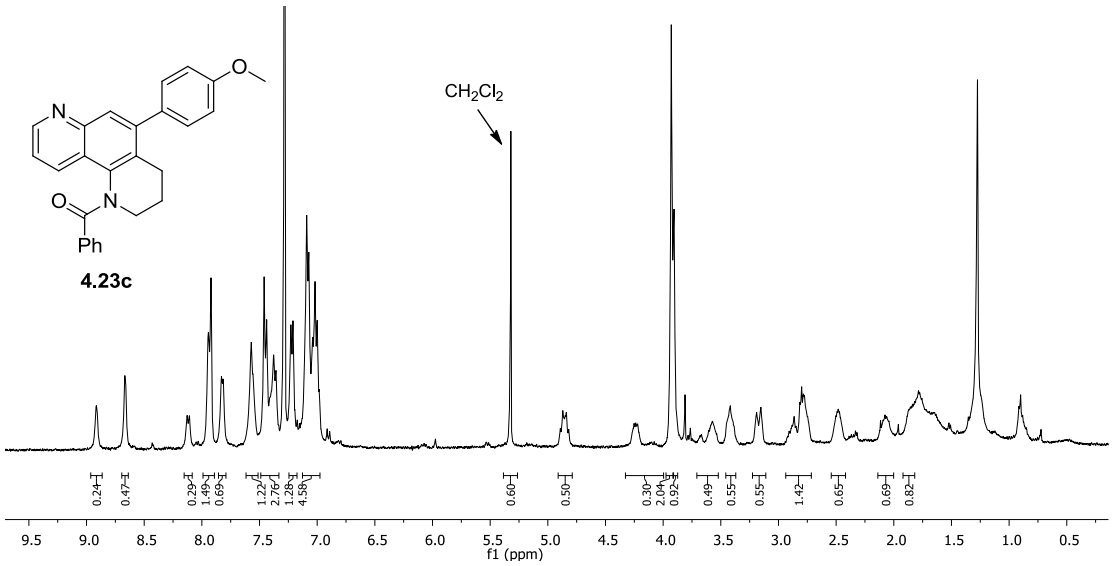

N
Ph
O
N
Ph
4.23a
^{1}H NMR in CD_3CN
At 25°C
At 50°C
At 65°C
At 75°C
f1 (ppm)

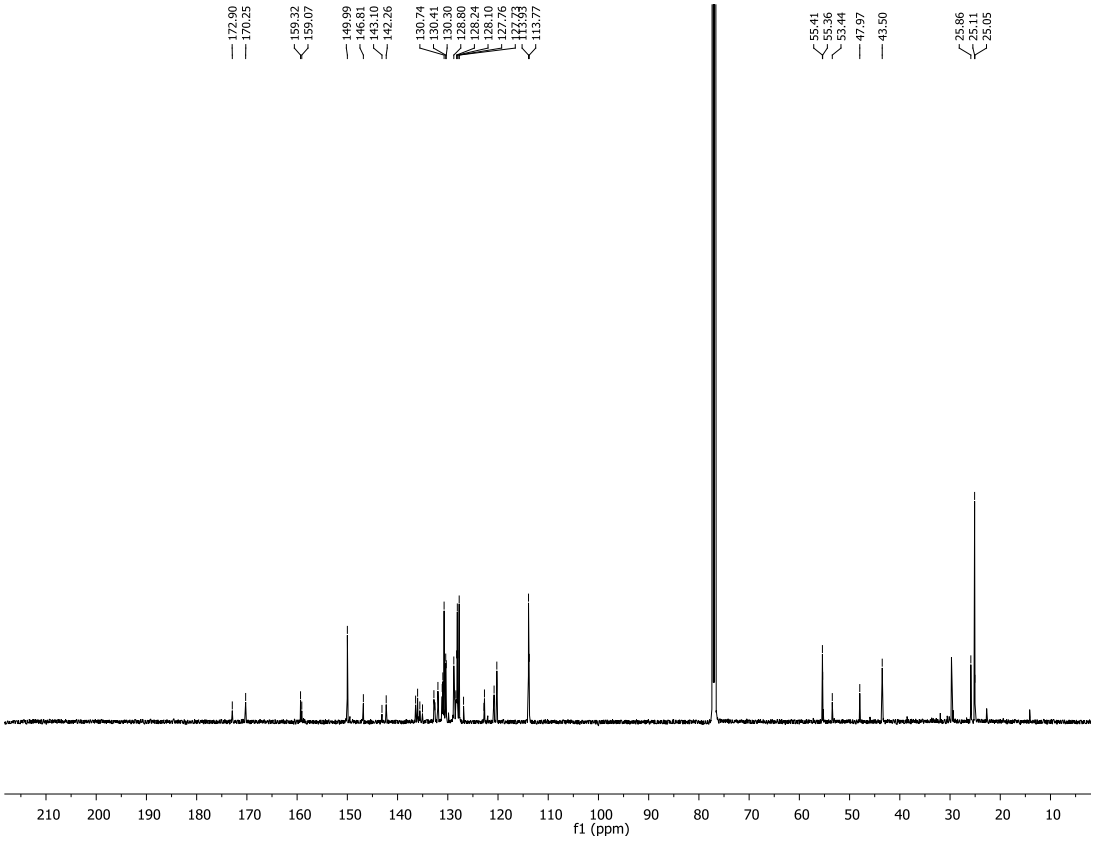

N
Ph
O
N
Ph
4.23a
^{1}H NMR in $CDCl_3$
0.21
0.39
0.33
1.51
0.78
7.11
0.67
1.18
1.16
1.15
0.50
0.36
0.38
0.54
0.53
1.49
0.64
0.57
1.35
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

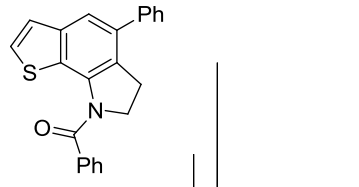

172.94
170.25
150.00
146.73
143.53
142.61
140.15
139.60
136.49
136.00
135.52
135.12
132.52
132.11
131.15
131.04
130.32
129.54
129.24
128.82
128.50
128.36
128.26
128.10
127.89
127.79
127.74
127.53
122.92
122.87
120.87
120.37
53.45
47.99
43.50
25.84
25.09
24.98
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F
N
O
N
Ph
4.23b
0.32
0.37
0.35
1.47
0.76
1.25
2.68
3.86
1.13
1.08
0.50
0.56
0.54
0.50
0.55
1.44
0.54
0.59
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

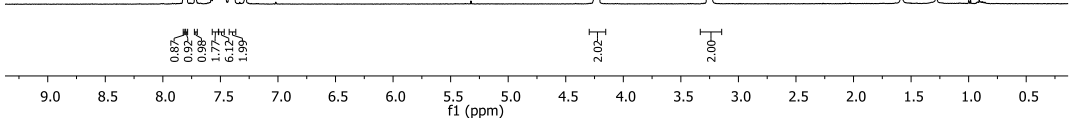

172.99
170.24
163.50
161.54
150.21
149.55
146.78
142.31
141.48
136.66
135.55
135.60
135.47
132.30
131.90
131.48
131.42
131.20
131.14
130.98
130.89
130.83
130.36
130.21
129.92
129.38
128.83
128.63
128.56
128.26
128.10
128.01
127.75
126.86
121.01
120.48
115.69
115.60
115.52
115.43
115.26
53.44
47.96
43.48
25.81
25.06
24.95
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

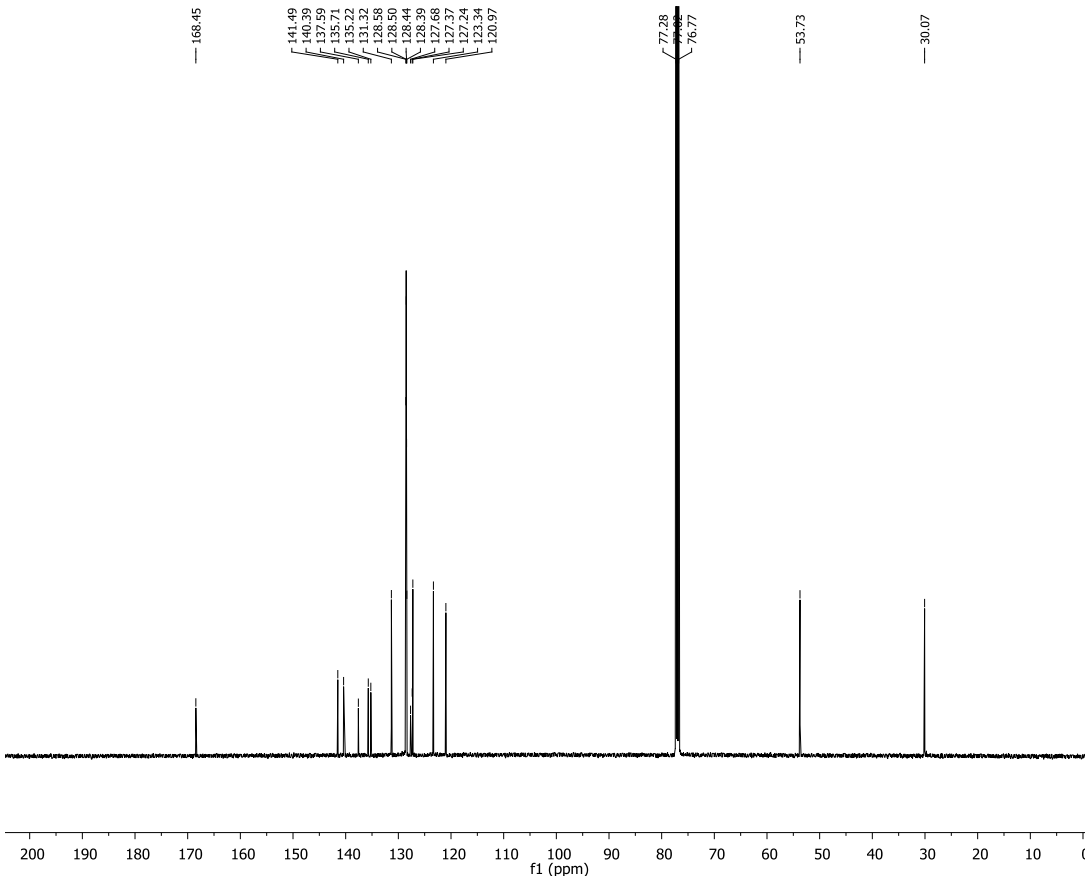

O
N
O
N
Ph
4.23c
CH_2Cl_2
0.24
0.47
0.29
1.49
0.69
1.22
2.76
1.28
4.58
0.60
0.50
0.30
2.04
0.92
0.49
0.55
0.55
1.42
0.65
0.69
0.82
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

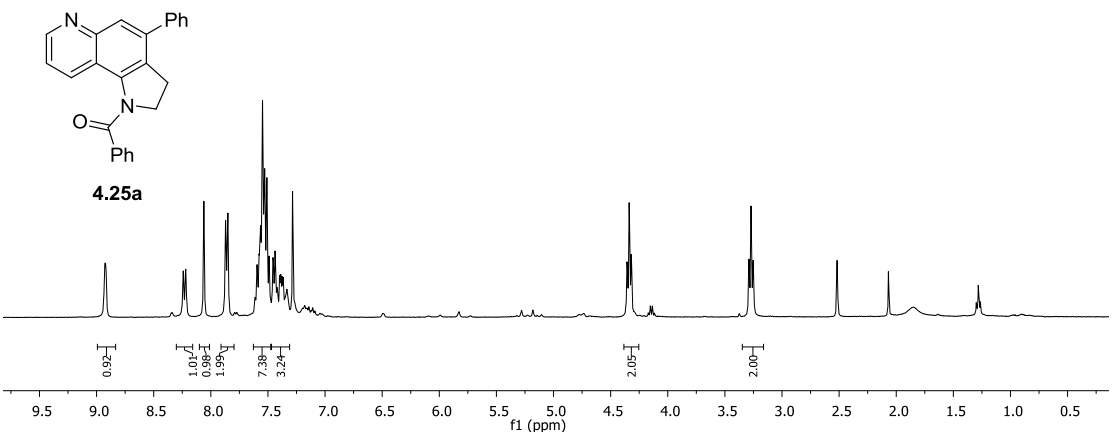

172.90
170.25
159.32
159.07
149.99
146.81
143.10
142.26
130.74
130.41
130.30
128.80
128.24
128.10
127.76
127.73
113.93
113.77
55.41
55.36
53.44
47.97
43.50
25.86
25.11
25.05
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

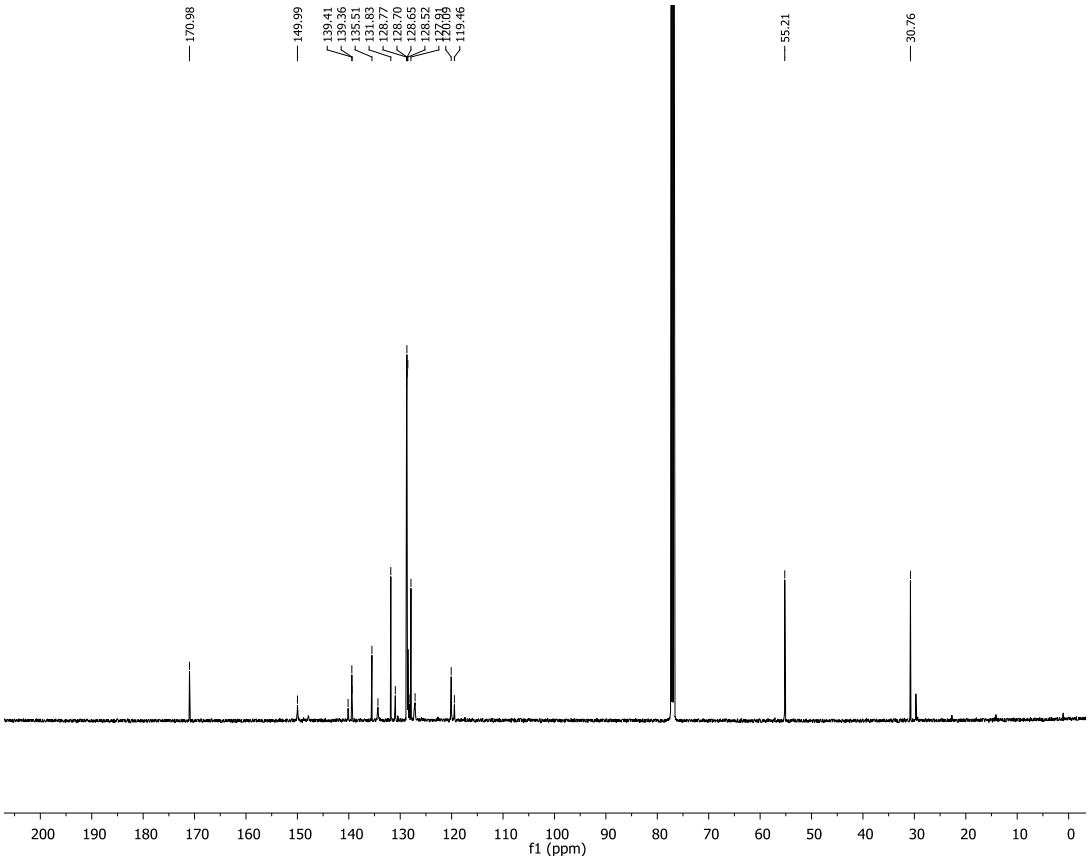

Ph
S
N
O
Ph

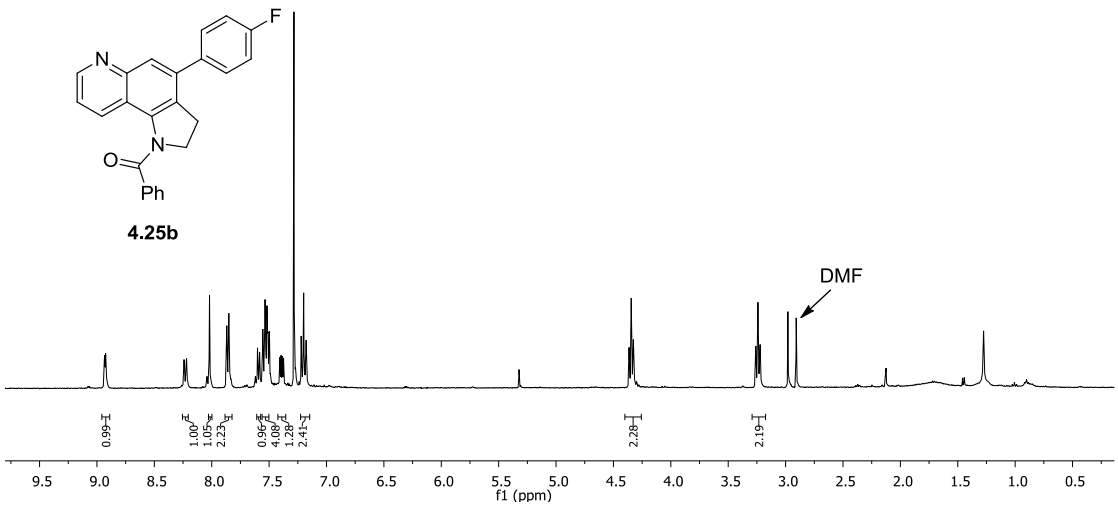
4.24

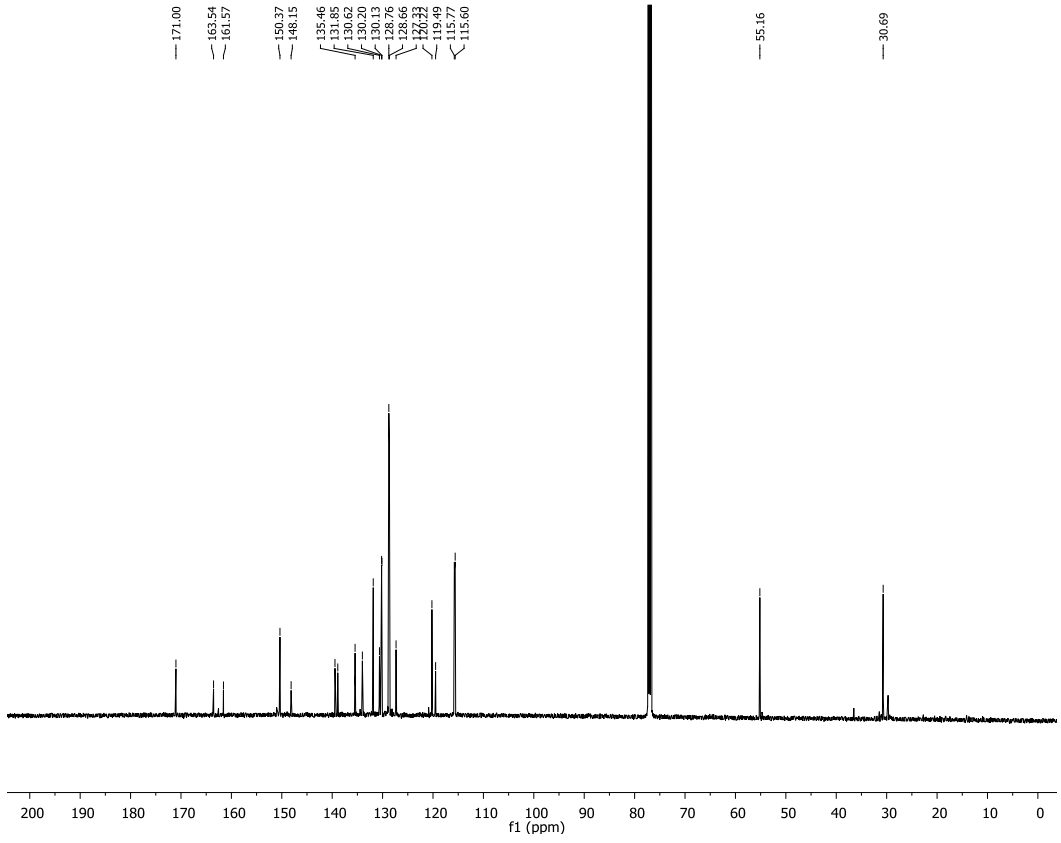

0.87
0.92
0.98
1.77
6.12
1.99
2.02
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

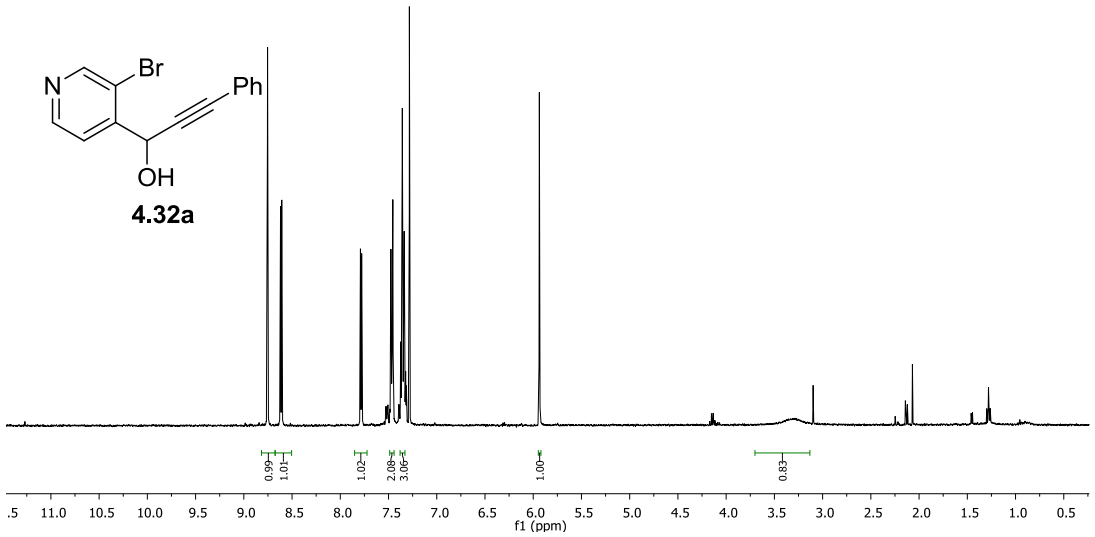

168.45
141.49
140.39
137.59
135.71
135.22
131.32
128.58
128.50
128.44
128.39
127.68
127.37
127.24
123.34
120.97
77.28
77.02
76.77
53.73
30.07
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

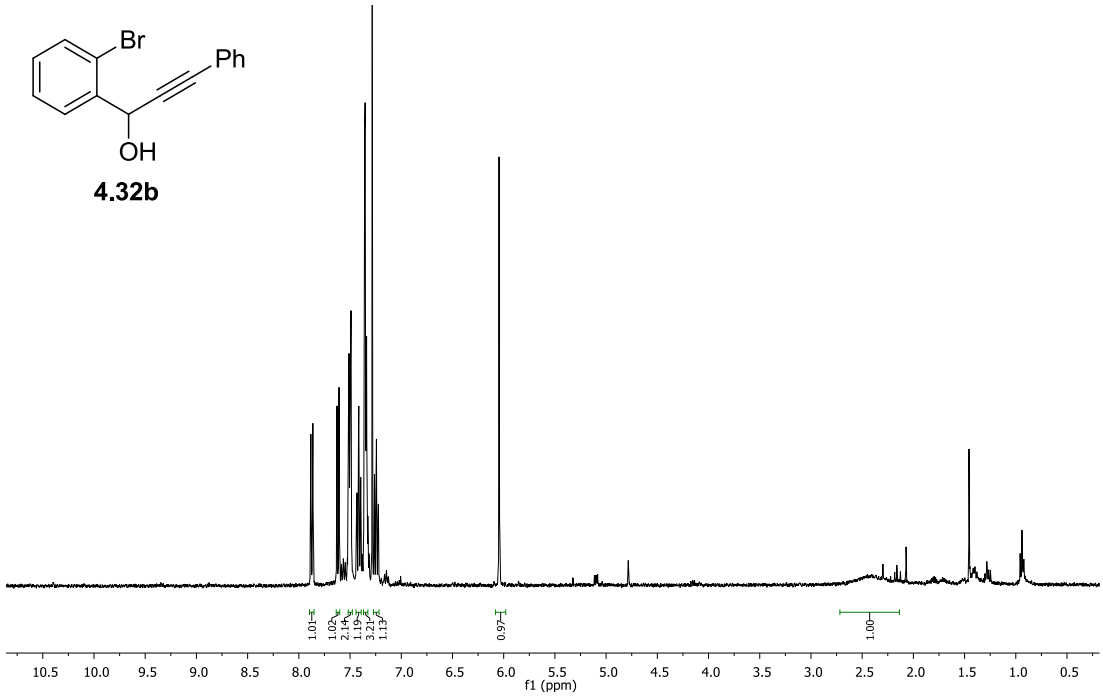

N
Ph
N
O
Ph
4.25a
0.92
1.01
0.98
1.99
7.38
3.24
2.05
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

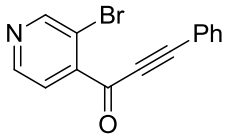

170.98
149.99
139.41
139.36
135.51
131.83
128.77
128.70
128.65
128.52
119.46
55.21
30.76
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F
N
N
O
Ph
4.25b
DMF
0.99
1.00
1.05
2.23
0.96
4.09
1.28
2.41
2.28
2.19
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

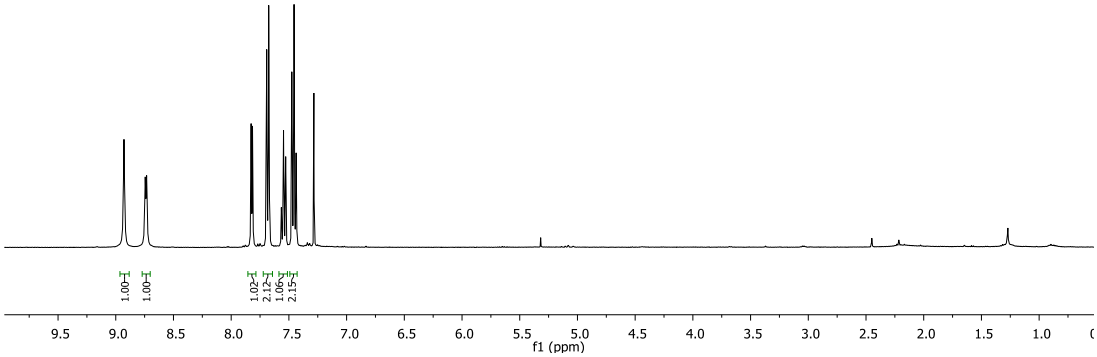

171.00
163.54
161.57
150.37
148.15
135.46
131.85
130.62
130.20
130.13
128.76
128.66
127.33
120.22
119.49
115.77
115.60
55.16
30.69
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

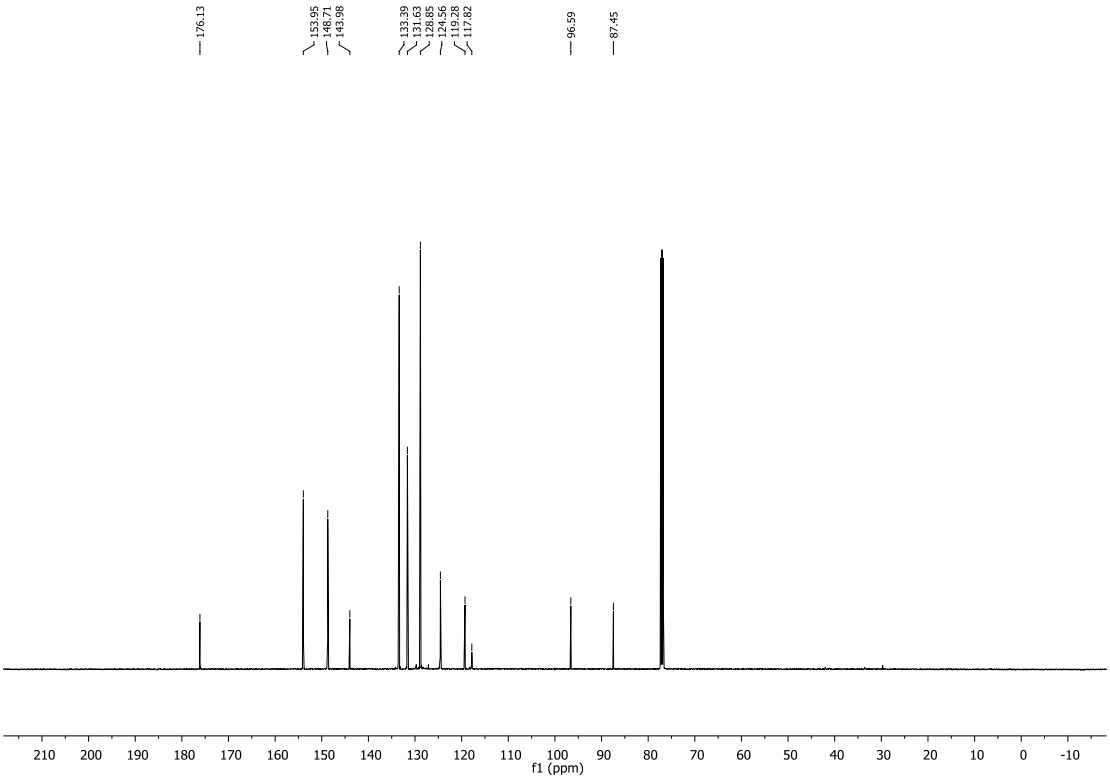

Br
N
Ph
OH
4.32a
0.99
1.01
1.02
2.09
3.06
1.00
0.83
f1 (ppm)

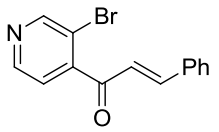

Br
Ph
OH
4.32b
1.01
1.02
2.14
1.19
3.22
1.13
0.97
1.00
f1 (ppm)


N
Br
Ph
O

4.40

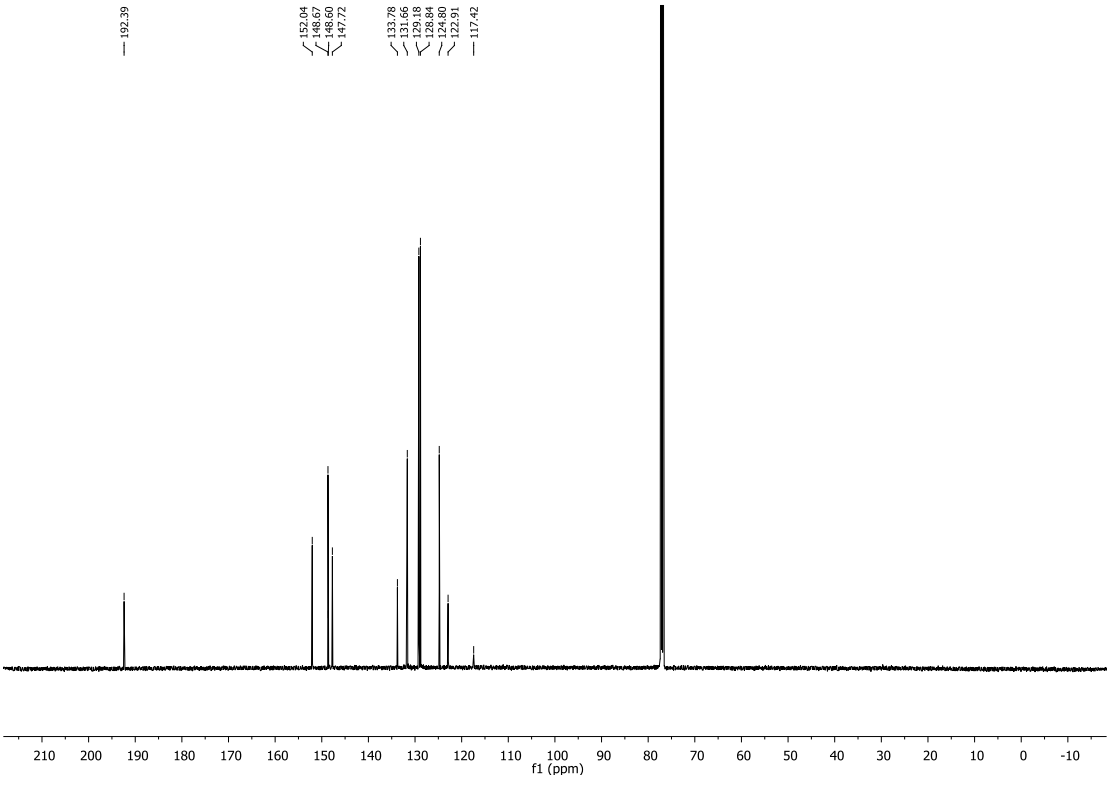

1.00
1.00
1.02
2.12
1.06
2.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

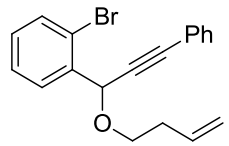

176.13
153.95
148.71
143.98
133.39
131.63
128.85
124.55
119.28
117.82
96.59
87.45
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


N
Br
Ph
O

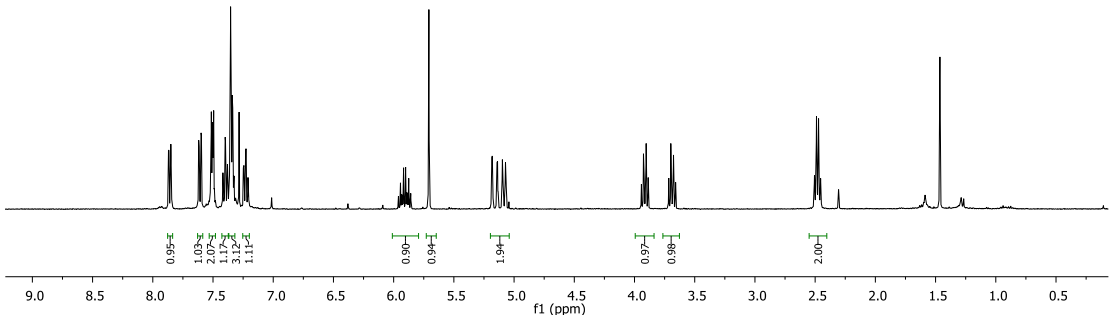
4.41

1.00
1.03
2.27
4.52
0.89
1.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

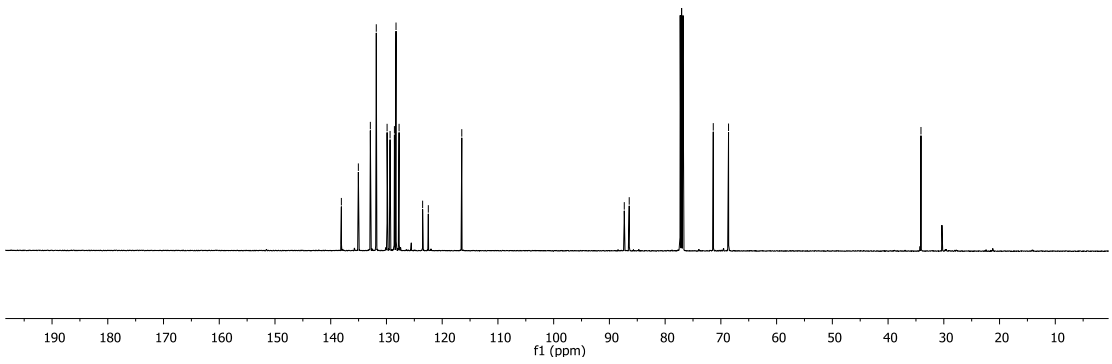

192.39
152.04
148.67
148.60
147.72
133.78
131.66
129.18
128.84
128.80
122.91
117.42
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

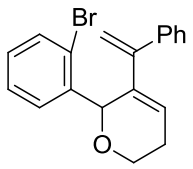

Br
Ph
O

4.42

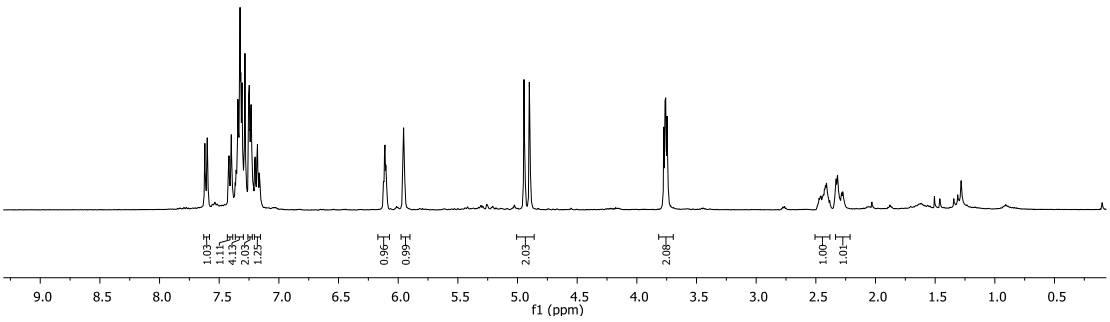

0.95
1.03
2.07
1.12
3.12
1.11
0.90
0.94
1.94
0.97
0.98
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

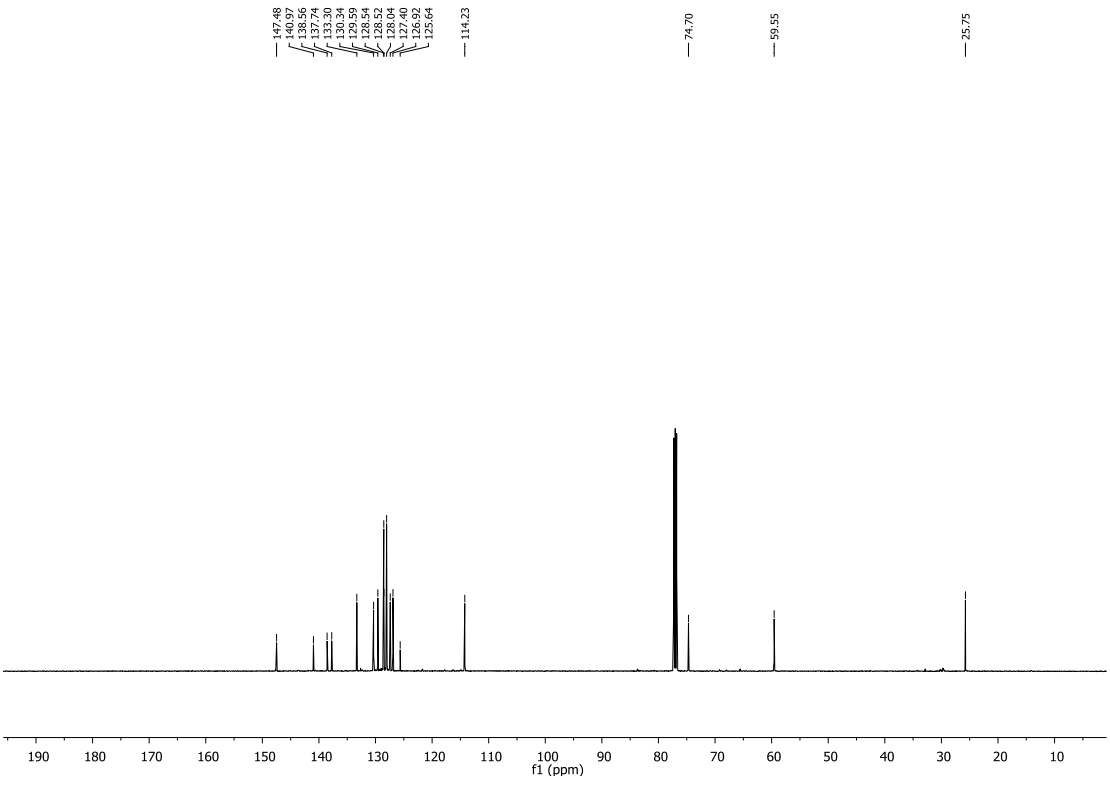

138.09
135.04
132.89
131.83
129.89
129.35
128.57
128.28
127.74
123.51
122.49
116.49
87.33
86.44
71.36
68.62
34.10

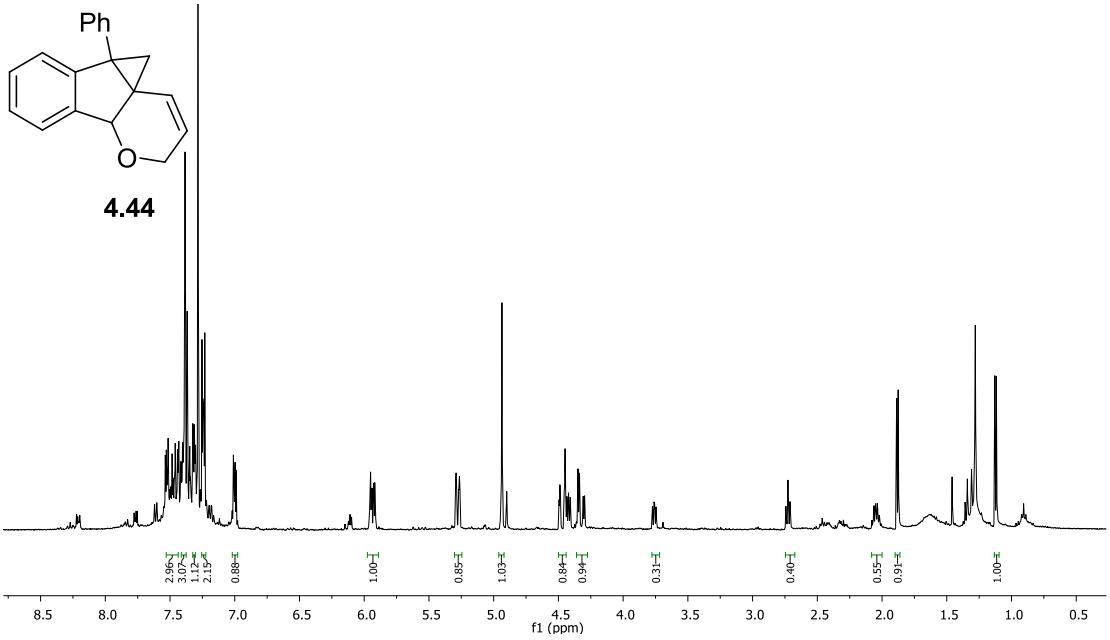

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Br
Ph
O

4.43


1.03
1.11
4.13
2.05
1.25
0.96
0.99
2.03
2.08
1.00
1.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

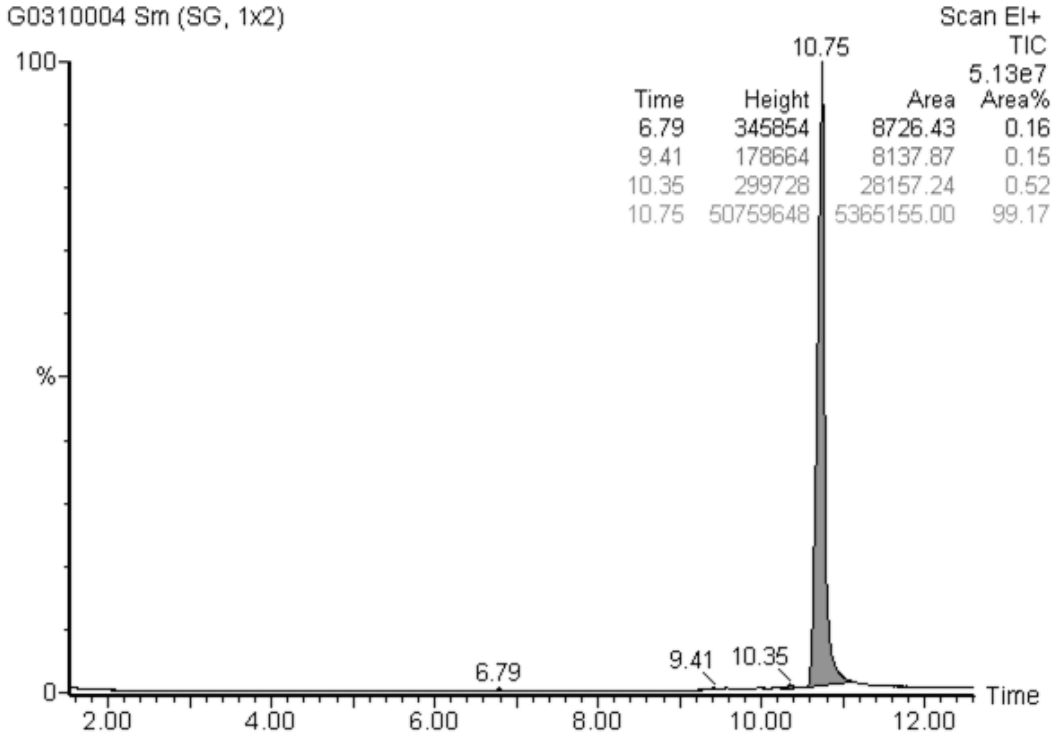

147.48
146.97
139.56
137.74
133.30
130.34
129.59
128.54
128.52
128.04
127.40
126.92
125.64
114.23
74.70
59.55
25.75
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



GC-MS spectras for compounds 4.23a-c and 4.25a-b:

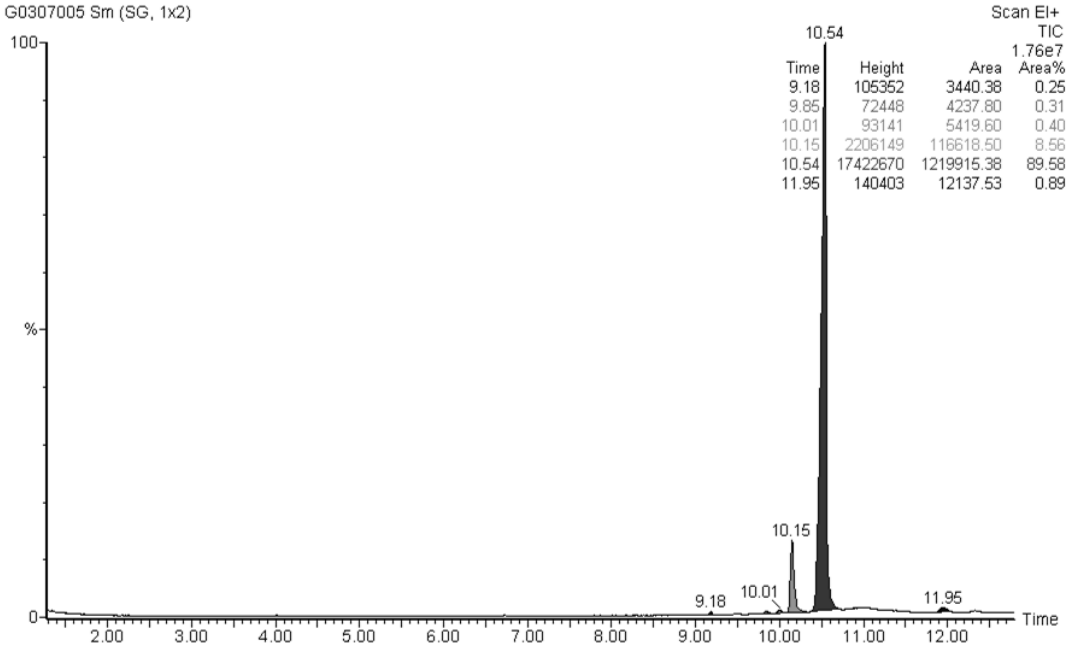
The GCMS data were collected on an Agilent 6890N gas chromatograph eluting into a QuattroMicro GC mass spectrometer (Micromass Ltd, Manchester UK). An HP-5MS, 15 meter column with a 0.25 ID was used. The carrier gas was Helium using constant flow control set to 1.5 mL per minute. 1.0µl of sample was injected into the column with a 20:1 split ratio. The injector port temperature was 240^{o}C. The chromatographic conditions were as follows: The initial column temperature was 50^{o}C with a 1 minute hold after which the temperature was increased 25^{o}C/min to a final temperature of 300^{o}C and held for 2 minutes. EI ionization was used with ion energy of 70V. The mass range was 45 to 400 m/z with a 0.3 scan time and an inter scan delay time of 0.07 seconds.

Pyrroloquinoline 4.25a **Quantitative integration table**

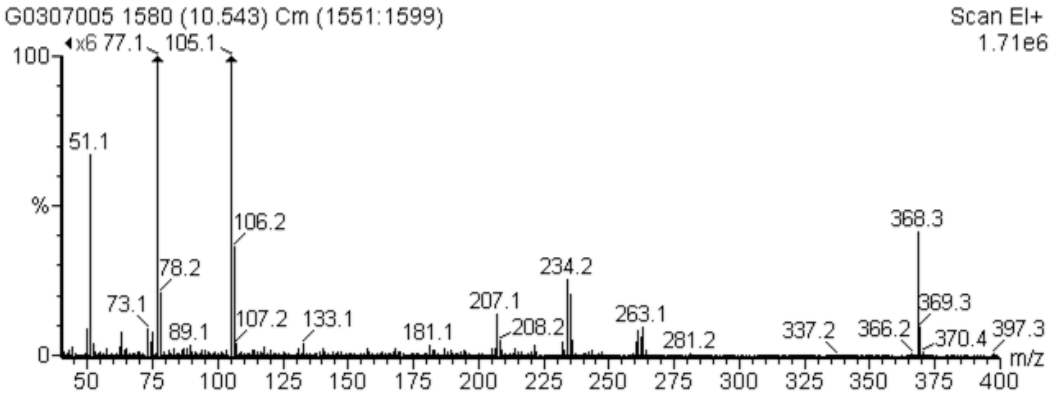


MS spectrum for the peak at 10.75 min retention time $C_{24}H_{18}N_2O$ = 350.1419

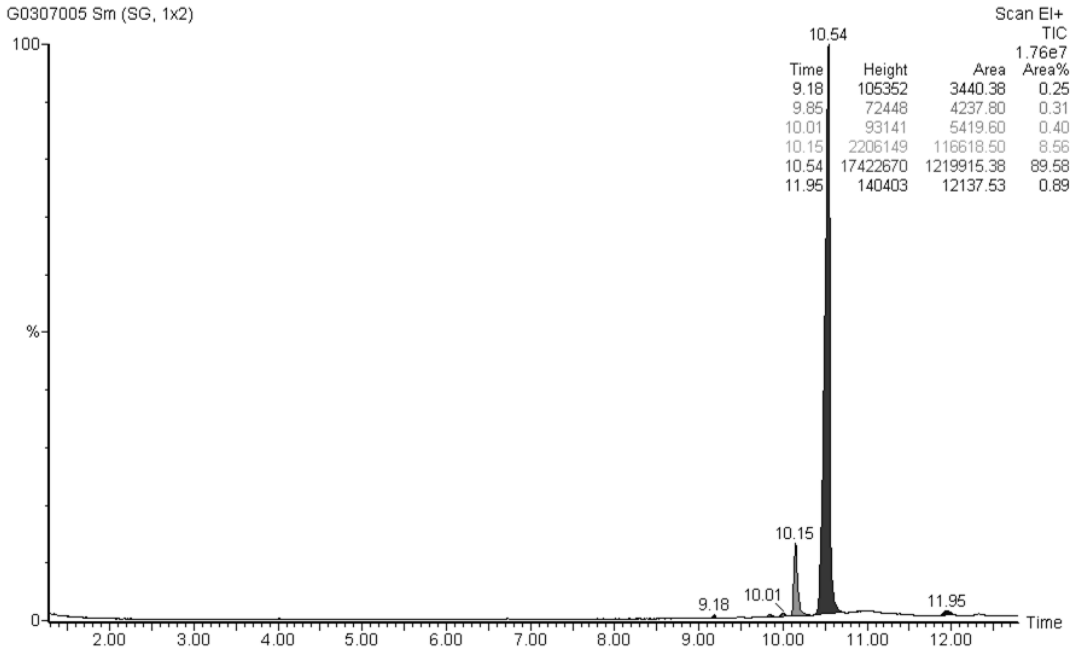
Pyrroloquinoline 4.25b **<u>Quantitative integration table</u>**



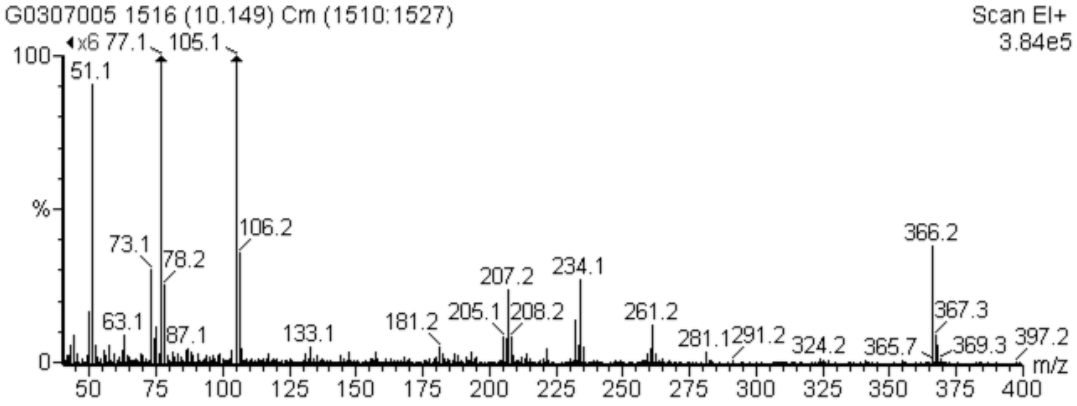
MS spectrum for the peak at 10.54 min retention time $C_{24}H_{17}FN_2O$ = 368.1325



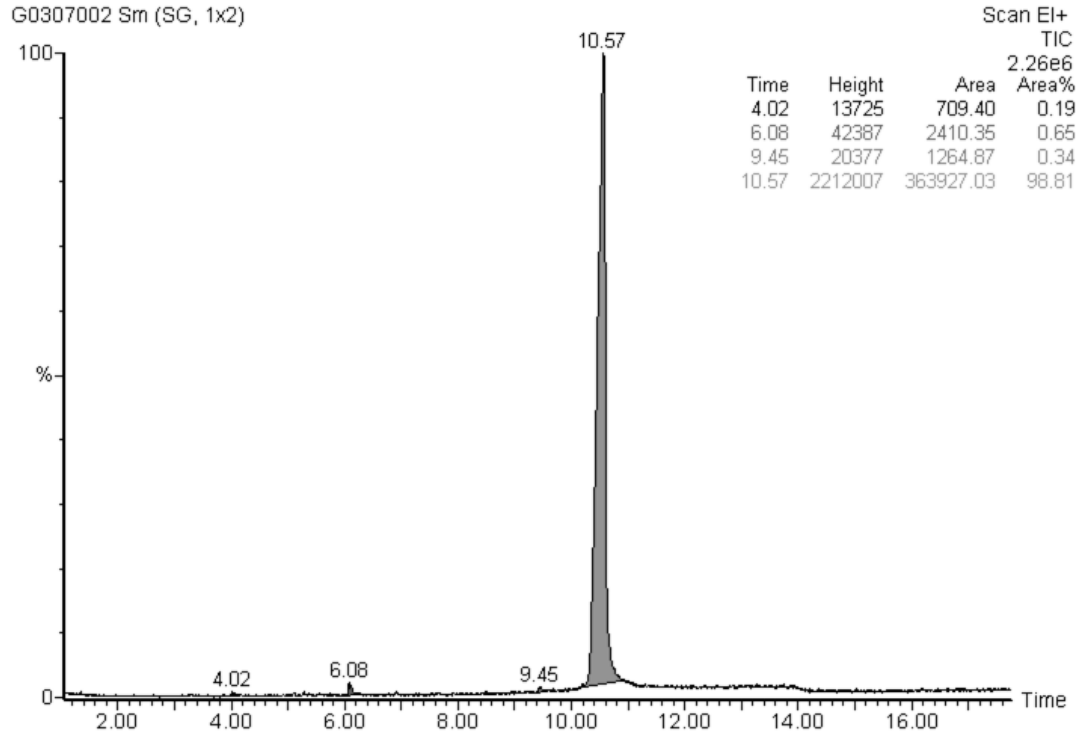
Oxidized pyrroloquinoline 4.25b **<u>Quantitative integration table</u>**



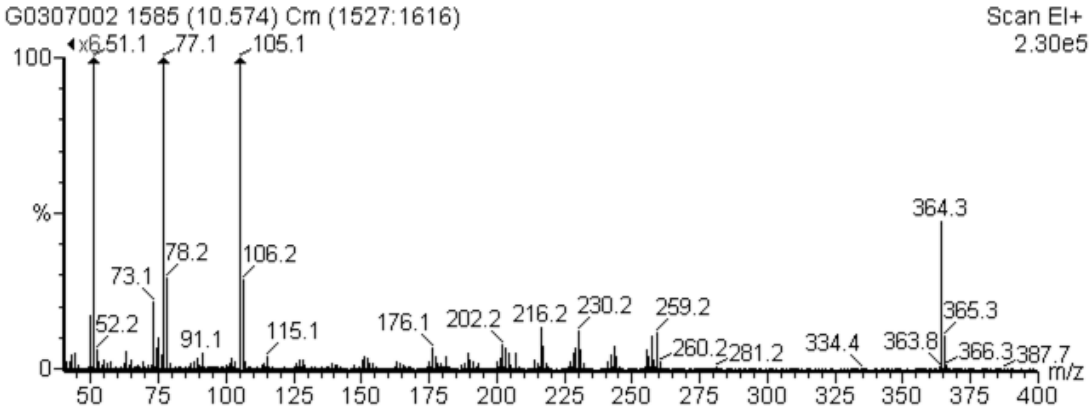
MS spectrum for the peak at 10.15 min retention time $C_{24}H_{15}FN_2O$ = 366.1168



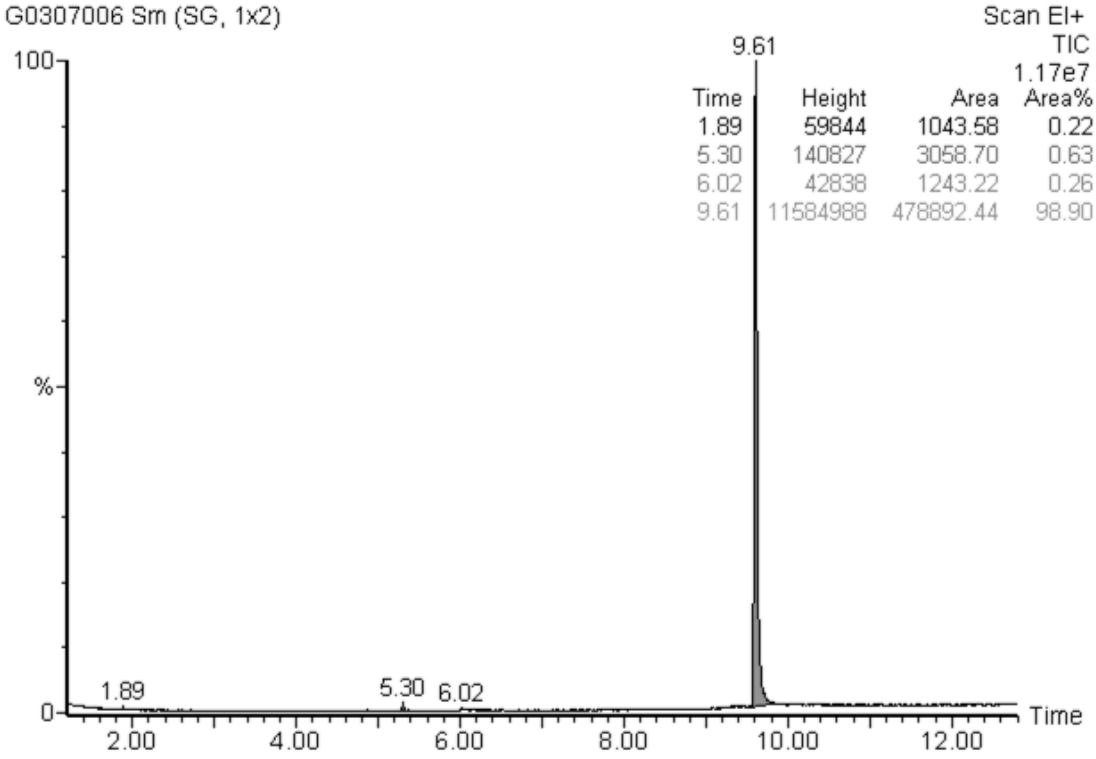
1,7-Phenanthroline 4.23a <u>Quantitative integration table</u>



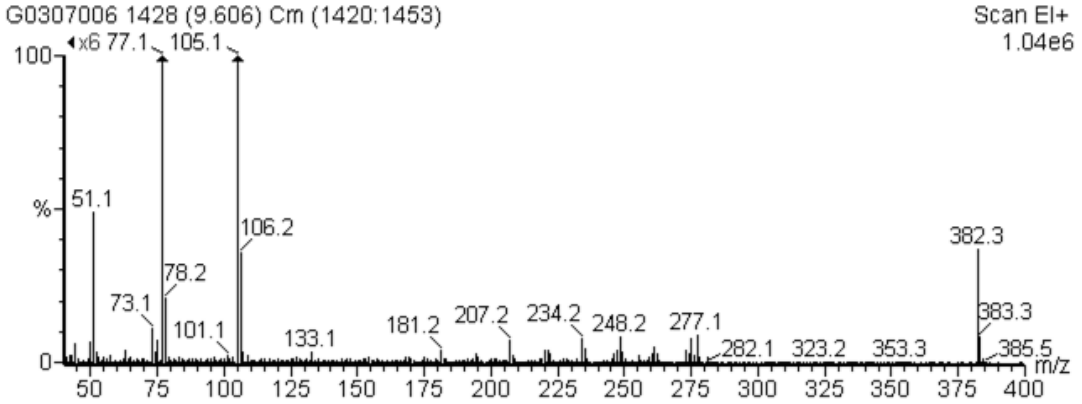
MS spectrum for the peak at 10.57 min retention time $C_{25}H_{20}N_2O$ = 364.1576



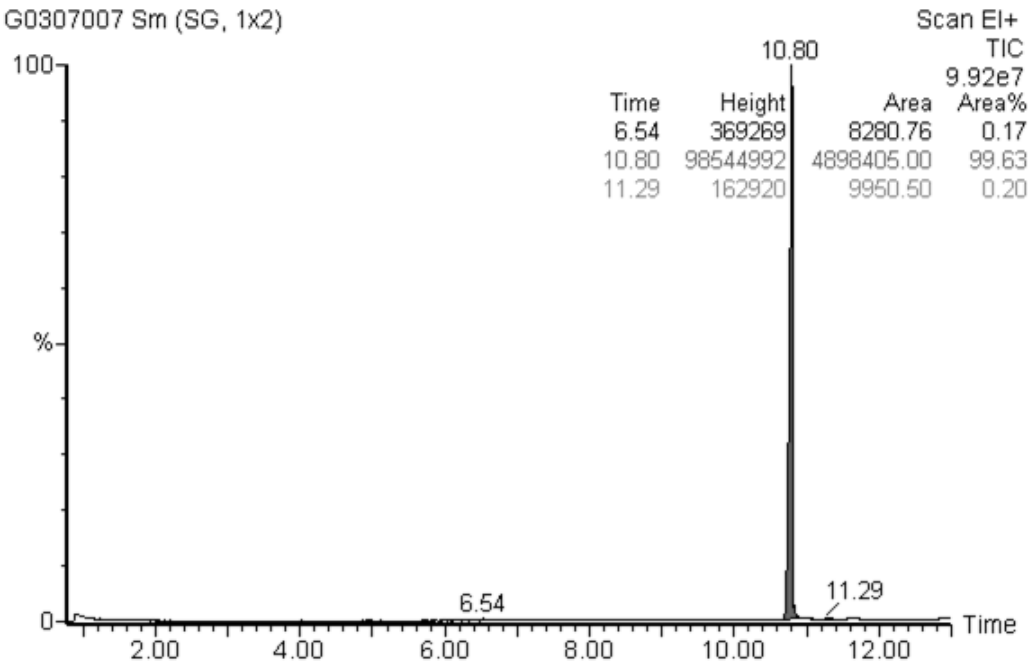
1,7-Phenanthroline 4.23b **Quantitative integration table**



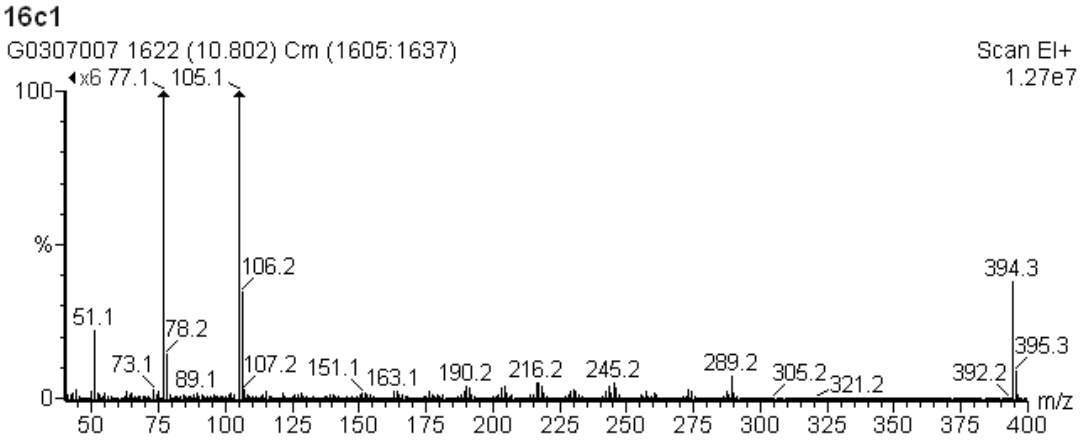
MS spectrum for the peak at 9.61 min retention time $C_{25}H_{19}FN_2O$ = 382.1481



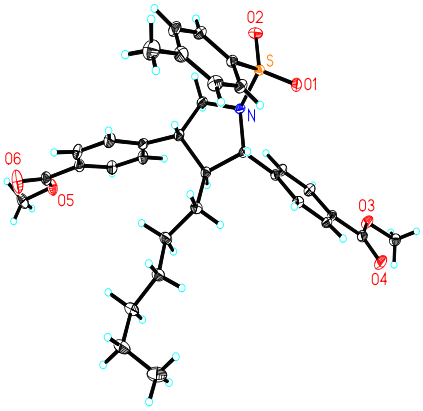
1,7-Phenanthroline 4.23c **Quantitative integration table**



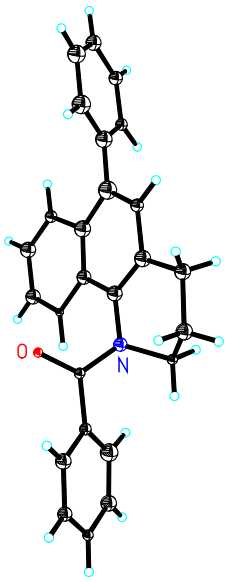
MS spectrum for the peak at 10.80 min retention time $C_{26}H_{22}N_2O_2$ = 394.1681



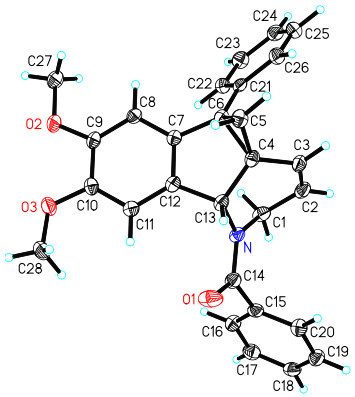
The thermal ellipsoids of **3.22**, **4.20**, **4.21b**, **4.22a** and **4.23a** drawn at 50% probability level.



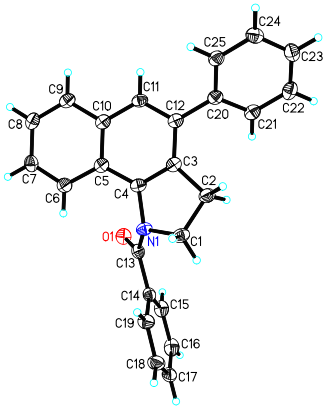
3.22 (CCDC 858605)



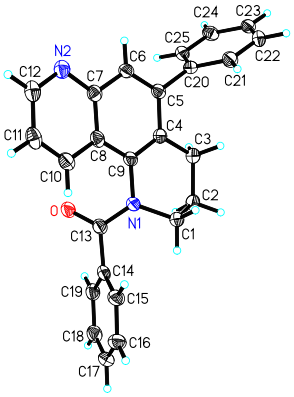
4.20 (CCDC 900884)



4.21b (CCDC 895234)



4.22a (CCDC 895235)



4.23a (CCDC 895233)

Acknowledgement: All the X ray analysis were performed by Dr. Victor Day

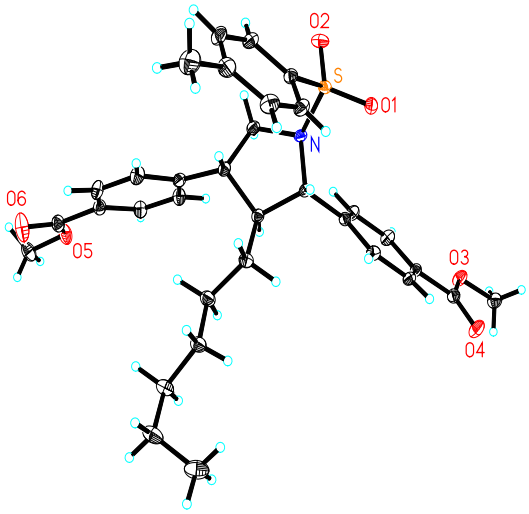


Table 1. Crystal data and structure refinement for $C_{33}H_{39}NO_6S$.

Identification code	k68f	
Empirical formula	$C_{33}H_{39}NO_6S$	
Formula weight	577.71	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 10.2039(6) Å	α= 90°.
	b = 26.1416(15) Å	β= 90°.
	c = 11.2558(7) Å	γ = 90°.
Volume	3002.4(3) $Å^3$	
Z	4	
Density (calculated)	1.278 Mg/m^3	

Absorption coefficient	0.153 mm^{-1}
F(000)	1232
Crystal size	0.32 x 0.32 x 0.20 mm^3
Theta range for data collection	2.53 to 30.53°.
Index ranges	-14<=h<=14, -37<=k<=37, -16<=l<=16
Reflections collected	34706
Independent reflections	9033 [R(int) = 0.0404]
Completeness to theta = 30.53°	99.4 %
Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.865
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9033 / 1 / 526
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1070
R indices (all data)	R1 = 0.0490, wR2 = 0.1081
Absolute structure parameter	0.06(5)
Largest diff. peak and hole	0.729 and -0.255 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C33H39NO6S. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)

S	5389(1)	4980(1)	4735(1)	14(1)
O(1)	4857(1)	5366(1)	3964(1)	19(1)
O(2)	5972(1)	5123(1)	5853(1)	20(1)
O(3)	-1713(1)	5911(1)	4597(1)	20(1)
O(4)	-1796(1)	5803(1)	2620(1)	23(1)
O(5)	2418(1)	1696(1)	7950(1)	24(1)
O(6)	3913(2)	1321(1)	6775(1)	35(1)
N	4175(1)	4593(1)	5046(1)	13(1)
C(1)	3327(1)	4438(1)	4021(1)	13(1)
C(2)	3039(2)	3864(1)	4246(1)	13(1)
C(3)	4230(1)	3684(1)	4976(1)	13(1)
C(4)	4467(2)	4142(1)	5804(1)	15(1)
C(5)	2107(1)	4763(1)	3925(1)	13(1)
C(6)	1642(2)	4909(1)	2806(1)	14(1)
C(7)	528(2)	5212(1)	2713(1)	14(1)
C(8)	-136(2)	5371(1)	3722(1)	13(1)
C(9)	315(2)	5223(1)	4844(2)	16(1)
C(10)	1429(2)	4916(1)	4940(1)	15(1)
C(11)	-1294(2)	5710(1)	3564(1)	16(1)
C(12)	-2830(2)	6249(1)	4498(2)	20(1)
C(13)	2808(2)	3579(1)	3074(1)	16(1)

C(14)	2140(2)	3057(1)	3178(2)	19(1)
C(15)	1934(2)	2812(1)	1961(2)	18(1)
C(16)	1120(2)	2322(1)	1989(2)	21(1)
C(17)	971(2)	2067(1)	771(2)	27(1)
C(18)	258(2)	2388(1)	-147(2)	30(1)
C(19)	4055(2)	3181(1)	5606(1)	14(1)
C(20)	4855(2)	2765(1)	5334(2)	18(1)
C(21)	4624(2)	2289(1)	5837(2)	19(1)
C(22)	3604(2)	2223(1)	6646(1)	16(1)
C(23)	2828(2)	2642(1)	6958(2)	18(1)
C(24)	3046(2)	3116(1)	6443(1)	17(1)
C(25)	3357(2)	1700(1)	7116(2)	19(1)
C(26)	2083(2)	1196(1)	8405(2)	24(1)
C(27)	6550(2)	4624(1)	3931(2)	15(1)
C(28)	6411(2)	4590(1)	2702(2)	18(1)
C(29)	7240(2)	4269(1)	2068(2)	22(1)
C(30)	8213(2)	3986(1)	2642(2)	23(1)
C(31)	8350(2)	4035(1)	3870(2)	22(1)
C(32)	7527(2)	4349(1)	4527(2)	18(1)
C(33)	9113(2)	3646(1)	1941(2)	32(1)

Table 3. Bond lengths [Å] and angles [°] for C33H39NO6S.

S-O(1)	1.4374(12)
S-O(2)	1.4408(13)
S-N	1.6373(13)
S-C(27)	1.7576(16)
O(3)-C(11)	1.345(2)
O(3)-C(12)	1.4457(19)
O(4)-C(11)	1.204(2)
O(5)-C(25)	1.342(2)
O(5)-C(26)	1.445(2)
O(6)-C(25)	1.202(2)
N-C(4)	1.4849(19)
N-C(1)	1.4987(19)
C(1)-C(5)	1.511(2)
C(1)-C(2)	1.549(2)
C(1)-H(1)	0.965(19)
C(2)-C(13)	1.534(2)
C(2)-C(3)	1.541(2)
C(2)-H(2)	1.00(2)
C(3)-C(19)	1.506(2)
C(3)-C(4)	1.537(2)

C(3)-H(3)	1.01(2)
C(4)-H(4A)	0.93(2)
C(4)-H(4B)	0.90(2)
C(5)-C(10)	1.395(2)
C(5)-C(6)	1.399(2)
C(6)-C(7)	1.390(2)
C(6)-H(6)	0.92(2)
C(7)-C(8)	1.387(2)
C(7)-H(7)	0.90(2)
C(8)-C(9)	1.399(2)
C(8)-C(11)	1.488(2)
C(9)-C(10)	1.396(2)
C(9)-H(9)	0.88(2)
C(10)-H(10)	0.96(2)
C(12)-H(12A)	0.93(2)
C(12)-H(12B)	0.86(2)
C(12)-H(12C)	0.87(3)
C(13)-C(14)	1.530(2)
C(13)-H(13A)	1.00(2)
C(13)-H(13B)	0.98(2)
C(14)-C(15)	1.527(2)
C(14)-H(14A)	1.01(3)

C(14)-H(14B)	1.07(2)
C(15)-C(16)	1.526(2)
C(15)-H(15A)	0.96(3)
C(15)-H(15B)	0.94(3)
C(16)-C(17)	1.532(3)
C(16)-H(16A)	0.88(3)
C(16)-H(16B)	1.04(2)
C(17)-C(18)	1.517(3)
C(17)-H(17A)	0.96(2)
C(17)-H(17B)	1.02(3)
C(18)-H(18A)	0.92(2)
C(18)-H(18B)	0.95(3)
C(18)-H(18C)	1.00(3)
C(19)-C(20)	1.394(2)
C(19)-C(24)	1.406(2)
C(20)-C(21)	1.386(2)
C(20)-H(20)	0.97(2)
C(21)-C(22)	1.394(2)
C(21)-H(21)	0.95(2)
C(22)-C(23)	1.396(2)
C(22)-C(25)	1.488(2)
C(23)-C(24)	1.386(2)

C(23)-H(23)	0.96(3)
C(24)-H(24)	0.95(2)
C(26)-H(26A)	0.96(3)
C(26)-H(26B)	0.85(3)
C(26)-H(26C)	0.93(3)
C(27)-C(28)	1.394(2)
C(27)-C(32)	1.400(2)
C(28)-C(29)	1.389(2)
C(28)-H(28)	0.86(2)
C(29)-C(30)	1.396(3)
C(29)-H(29)	0.98(2)
C(30)-C(31)	1.395(3)
C(30)-C(33)	1.502(3)
C(31)-C(32)	1.390(2)
C(31)-H(31)	0.91(2)
C(32)-H(32)	0.84(2)
C(33)-H(33A)	0.89(3)
C(33)-H(33B)	0.95(4)
C(33)-H(33C)	0.90(4)

O(1)-S-O(2)	120.10(7)
O(1)-S-N	106.05(7)

O(2)-S-N	106.65(7)
O(1)-S-C(27)	108.34(8)
O(2)-S-C(27)	107.98(8)
N-S-C(27)	107.05(7)
C(11)-O(3)-C(12)	114.97(13)
C(25)-O(5)-C(26)	115.05(14)
C(4)-N-C(1)	110.09(12)
C(4)-N-S	117.45(10)
C(1)-N-S	116.09(10)
N-C(1)-C(5)	112.21(12)
N-C(1)-C(2)	104.21(12)
C(5)-C(1)-C(2)	113.62(12)
N-C(1)-H(1)	110.4(11)
C(5)-C(1)-H(1)	109.1(11)
C(2)-C(1)-H(1)	107.1(11)
C(13)-C(2)-C(3)	115.50(13)
C(13)-C(2)-C(1)	111.05(12)
C(3)-C(2)-C(1)	103.50(12)
C(13)-C(2)-H(2)	108.3(13)
C(3)-C(2)-H(2)	109.8(13)
C(1)-C(2)-H(2)	108.5(12)
C(19)-C(3)-C(4)	114.48(12)

C(19)-C(3)-C(2)	115.12(12)
C(4)-C(3)-C(2)	102.08(12)
C(19)-C(3)-H(3)	109.9(11)
C(4)-C(3)-H(3)	107.3(12)
C(2)-C(3)-H(3)	107.3(11)
N-C(4)-C(3)	103.79(12)
N-C(4)-H(4A)	107.8(13)
C(3)-C(4)-H(4A)	111.4(13)
N-C(4)-H(4B)	108.9(13)
C(3)-C(4)-H(4B)	111.2(13)
H(4A)-C(4)-H(4B)	113.3(19)
C(10)-C(5)-C(6)	119.46(13)
C(10)-C(5)-C(1)	120.73(13)
C(6)-C(5)-C(1)	119.80(14)
C(7)-C(6)-C(5)	120.05(14)
C(7)-C(6)-H(6)	119.8(12)
C(5)-C(6)-H(6)	120.2(12)
C(8)-C(7)-C(6)	120.61(14)
C(8)-C(7)-H(7)	120.2(13)
C(6)-C(7)-H(7)	119.0(13)
C(7)-C(8)-C(9)	119.71(13)
C(7)-C(8)-C(11)	118.00(14)

C(9)-C(8)-C(11)	122.27(14)
C(10)-C(9)-C(8)	119.84(15)
C(10)-C(9)-H(9)	118.3(15)
C(8)-C(9)-H(9)	121.8(15)
C(5)-C(10)-C(9)	120.31(14)
C(5)-C(10)-H(10)	118.1(14)
C(9)-C(10)-H(10)	121.6(14)
O(4)-C(11)-O(3)	123.27(14)
O(4)-C(11)-C(8)	124.30(15)
O(3)-C(11)-C(8)	112.42(13)
O(3)-C(12)-H(12A)	110.3(13)
O(3)-C(12)-H(12B)	110.4(14)
H(12A)-C(12)-H(12B)	109.8(19)
O(3)-C(12)-H(12C)	102.2(16)
H(12A)-C(12)-H(12C)	113(2)
H(12B)-C(12)-H(12C)	111(2)
C(14)-C(13)-C(2)	115.90(13)
C(14)-C(13)-H(13A)	108.1(12)
C(2)-C(13)-H(13A)	107.5(12)
C(14)-C(13)-H(13B)	111.3(12)
C(2)-C(13)-H(13B)	107.3(13)
H(13A)-C(13)-H(13B)	106.3(18)

C(15)-C(14)-C(13)	111.56(14)
C(15)-C(14)-H(14A)	108.5(14)
C(13)-C(14)-H(14A)	111.6(14)
C(15)-C(14)-H(14B)	109.3(12)
C(13)-C(14)-H(14B)	110.3(12)
H(14A)-C(14)-H(14B)	105.4(18)
C(16)-C(15)-C(14)	114.09(15)
C(16)-C(15)-H(15A)	110.5(15)
C(14)-C(15)-H(15A)	110.2(16)
C(16)-C(15)-H(15B)	109.2(15)
C(14)-C(15)-H(15B)	109.7(15)
H(15A)-C(15)-H(15B)	102(2)
C(15)-C(16)-C(17)	113.56(15)
C(15)-C(16)-H(16A)	108.0(16)
C(17)-C(16)-H(16A)	109.6(17)
C(15)-C(16)-H(16B)	104.8(13)
C(17)-C(16)-H(16B)	114.0(14)
H(16A)-C(16)-H(16B)	106(2)
C(18)-C(17)-C(16)	114.64(16)
C(18)-C(17)-H(17A)	110.4(15)
C(16)-C(17)-H(17A)	107.3(15)
C(18)-C(17)-H(17B)	106.8(15)

C(16)-C(17)-H(17B)	113.7(15)
H(17A)-C(17)-H(17B)	103(2)
C(17)-C(18)-H(18A)	107.4(16)
C(17)-C(18)-H(18B)	110(2)
H(18A)-C(18)-H(18B)	105(2)
C(17)-C(18)-H(18C)	111.8(15)
H(18A)-C(18)-H(18C)	111(2)
H(18B)-C(18)-H(18C)	111(3)
C(20)-C(19)-C(24)	118.82(14)
C(20)-C(19)-C(3)	120.61(14)
C(24)-C(19)-C(3)	120.52(13)
C(21)-C(20)-C(19)	120.66(15)
C(21)-C(20)-H(20)	119.7(13)
C(19)-C(20)-H(20)	119.5(13)
C(20)-C(21)-C(22)	120.36(15)
C(20)-C(21)-H(21)	121.0(13)
C(22)-C(21)-H(21)	118.4(13)
C(21)-C(22)-C(23)	119.40(14)
C(21)-C(22)-C(25)	118.18(14)
C(23)-C(22)-C(25)	122.39(15)
C(24)-C(23)-C(22)	120.27(15)
C(24)-C(23)-H(23)	120.5(14)

C(22)-C(23)-H(23)	119.1(14)
C(23)-C(24)-C(19)	120.42(15)
C(23)-C(24)-H(24)	119.6(13)
C(19)-C(24)-H(24)	120.0(13)
O(6)-C(25)-O(5)	123.65(15)
O(6)-C(25)-C(22)	124.29(16)
O(5)-C(25)-C(22)	112.05(14)
O(5)-C(26)-H(26A)	104.7(15)
O(5)-C(26)-H(26B)	114.5(17)
H(26A)-C(26)-H(26B)	104(2)
O(5)-C(26)-H(26C)	109.4(15)
H(26A)-C(26)-H(26C)	113(2)
H(26B)-C(26)-H(26C)	112(2)
C(28)-C(27)-C(32)	121.01(15)
C(28)-C(27)-S	118.48(12)
C(32)-C(27)-S	120.31(13)
C(29)-C(28)-C(27)	119.12(15)
C(29)-C(28)-H(28)	117.7(15)
C(27)-C(28)-H(28)	123.1(15)
C(28)-C(29)-C(30)	121.05(16)
C(28)-C(29)-H(29)	120.3(13)
C(30)-C(29)-H(29)	118.7(13)

C(31)-C(30)-C(29)	118.76(16)
C(31)-C(30)-C(33)	120.85(18)
C(29)-C(30)-C(33)	120.37(18)
C(32)-C(31)-C(30)	121.39(16)
C(32)-C(31)-H(31)	119.2(14)
C(30)-C(31)-H(31)	119.3(14)
C(31)-C(32)-C(27)	118.65(16)
C(31)-C(32)-H(32)	121.2(15)
C(27)-C(32)-H(32)	120.1(15)
C(30)-C(33)-H(33A)	108.7(19)
C(30)-C(33)-H(33B)	118(2)
H(33A)-C(33)-H(33B)	108(3)
C(30)-C(33)-H(33C)	108(2)
H(33A)-C(33)-H(33C)	104(3)
H(33B)-C(33)-H(33C)	109(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for C33H39NO6S. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	11(1)	14(1)	16(1)	0(1)	0(1)	-1(1)
O(1)	16(1)	15(1)	26(1)	3(1)	-2(1)	1(1)
O(2)	16(1)	24(1)	19(1)	-5(1)	-2(1)	-4(1)
O(3)	17(1)	24(1)	17(1)	-1(1)	-2(1)	7(1)
O(4)	20(1)	27(1)	21(1)	-1(1)	-5(1)	9(1)
O(5)	27(1)	16(1)	29(1)	3(1)	8(1)	-1(1)
O(6)	50(1)	18(1)	35(1)	5(1)	17(1)	8(1)
N	10(1)	15(1)	14(1)	1(1)	-2(1)	-1(1)
C(1)	11(1)	15(1)	12(1)	1(1)	0(1)	1(1)
C(2)	11(1)	14(1)	14(1)	0(1)	1(1)	1(1)
C(3)	11(1)	15(1)	14(1)	2(1)	1(1)	1(1)
C(4)	14(1)	17(1)	14(1)	2(1)	-2(1)	0(1)
C(5)	11(1)	12(1)	15(1)	1(1)	0(1)	0(1)
C(6)	14(1)	17(1)	13(1)	-1(1)	1(1)	0(1)
C(7)	15(1)	15(1)	13(1)	0(1)	-3(1)	1(1)
C(8)	10(1)	13(1)	15(1)	2(1)	0(1)	1(1)
C(9)	14(1)	21(1)	13(1)	1(1)	2(1)	2(1)

C(10)	15(1)	18(1)	12(1)	2(1)	0(1)	2(1)
C(11)	12(1)	16(1)	19(1)	1(1)	0(1)	0(1)
C(12)	17(1)	20(1)	23(1)	-4(1)	-1(1)	5(1)
C(13)	16(1)	16(1)	16(1)	-1(1)	-1(1)	-1(1)
C(14)	21(1)	17(1)	18(1)	-2(1)	-2(1)	-2(1)
C(15)	15(1)	19(1)	22(1)	-5(1)	0(1)	0(1)
C(16)	21(1)	21(1)	22(1)	-4(1)	0(1)	-5(1)
C(17)	28(1)	26(1)	28(1)	-11(1)	1(1)	-6(1)
C(18)	26(1)	43(1)	21(1)	-7(1)	2(1)	-8(1)
C(19)	13(1)	16(1)	14(1)	2(1)	-1(1)	0(1)
C(20)	15(1)	21(1)	18(1)	3(1)	5(1)	3(1)
C(21)	19(1)	18(1)	22(1)	2(1)	2(1)	7(1)
C(22)	18(1)	15(1)	15(1)	1(1)	0(1)	1(1)
C(23)	18(1)	17(1)	18(1)	2(1)	4(1)	1(1)
C(24)	17(1)	17(1)	18(1)	0(1)	5(1)	3(1)
C(25)	25(1)	15(1)	18(1)	3(1)	-1(1)	0(1)
C(26)	32(1)	16(1)	24(1)	2(1)	5(1)	-6(1)
C(27)	11(1)	16(1)	18(1)	1(1)	1(1)	1(1)
C(28)	14(1)	22(1)	18(1)	4(1)	0(1)	1(1)
C(29)	17(1)	27(1)	20(1)	-1(1)	3(1)	0(1)
C(30)	15(1)	22(1)	30(1)	-2(1)	5(1)	1(1)
C(31)	13(1)	22(1)	32(1)	3(1)	0(1)	5(1)

C(32)	15(1)	22(1)	17(1)	3(1)	-2(1)	1(1)
C(33)	22(1)	35(1)	39(1)	-8(1)	6(1)	9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C33H39NO6S.

	x	y	z	U(eq)
H(1)	3810(19)	4459(7)	3285(17)	7(4)
H(2)	2220(20)	3837(8)	4740(20)	23(5)
H(3)	5000(20)	3664(8)	4417(18)	17(5)
H(4A)	3880(20)	4144(8)	6440(20)	19(5)
H(4B)	5310(20)	4158(8)	6036(19)	17(5)
H(6)	2076(19)	4808(7)	2131(18)	8(4)
H(7)	280(20)	5324(7)	1993(19)	12(5)
H(9)	-80(20)	5324(8)	5500(20)	20(5)
H(10)	1750(20)	4801(8)	5700(20)	21(5)
H(12A)	-2580(20)	6560(8)	4169(18)	15(5)
H(12B)	-3430(20)	6110(8)	4070(20)	19(5)
H(12C)	-3080(20)	6276(9)	5240(20)	27(6)
H(13A)	2250(20)	3803(7)	2560(20)	16(5)

H(13B)	3660(20)	3551(8)	2673(19)	19(5)
H(14A)	2670(20)	2813(9)	3690(20)	31(6)
H(14B)	1220(20)	3094(8)	3610(20)	21(5)
H(15A)	2760(30)	2751(9)	1580(20)	33(6)
H(15B)	1530(30)	3048(9)	1440(20)	33(6)
H(16A)	340(20)	2398(9)	2280(20)	29(6)
H(16B)	1570(20)	2093(9)	2620(20)	29(6)
H(17A)	520(20)	1748(9)	890(20)	26(6)
H(17B)	1840(30)	1959(10)	400(20)	35(7)
H(18A)	-520(20)	2487(9)	180(20)	26(6)
H(18B)	720(30)	2697(13)	-290(30)	67(10)
H(18C)	120(30)	2196(10)	-900(30)	35(7)
H(20)	5550(20)	2804(9)	4750(20)	26(5)
H(21)	5100(20)	1995(8)	5588(19)	17(5)
H(23)	2180(20)	2603(9)	7580(20)	27(6)
H(24)	2510(20)	3397(9)	6660(20)	20(5)
H(26A)	1320(20)	1252(9)	8880(30)	35(6)
H(26B)	1820(20)	985(10)	7880(20)	30(6)
H(26C)	2780(20)	1067(9)	8840(20)	30(6)
H(28)	5800(20)	4742(8)	2320(20)	21(5)
H(29)	7160(20)	4239(8)	1200(20)	21(5)
H(31)	9030(20)	3875(8)	4240(20)	22(5)

H(32)	7610(20)	4376(8)	5270(20)	19(5)
H(33A)	9930(30)	3755(10)	2030(30)	47(8)
H(33B)	8950(40)	3609(14)	1110(40)	86(13)
H(33C)	9120(30)	3333(14)	2280(30)	63(10)

Table 6. Torsion angles [°] for C33H39NO6S.

O(1)-S-N-C(4)	177.80(11)
O(2)-S-N-C(4)	-53.11(13)
C(27)-S-N-C(4)	62.28(13)
O(1)-S-N-C(1)	44.53(12)
O(2)-S-N-C(1)	173.62(10)
C(27)-S-N-C(1)	-70.99(12)
C(4)-N-C(1)-C(5)	127.01(13)
S-N-C(1)-C(5)	-96.46(13)
C(4)-N-C(1)-C(2)	3.65(15)
S-N-C(1)-C(2)	140.18(10)
N-C(1)-C(2)-C(13)	-151.42(12)
C(5)-C(1)-C(2)-C(13)	86.15(16)
N-C(1)-C(2)-C(3)	-26.89(14)
C(5)-C(1)-C(2)-C(3)	-149.33(13)

C(13)-C(2)-C(3)-C(19)	-74.28(16)
C(1)-C(2)-C(3)-C(19)	164.13(12)
C(13)-C(2)-C(3)-C(4)	161.09(13)
C(1)-C(2)-C(3)-C(4)	39.50(14)
C(1)-N-C(4)-C(3)	21.10(15)
S-N-C(4)-C(3)	-114.77(12)
C(19)-C(3)-C(4)-N	-162.21(12)
C(2)-C(3)-C(4)-N	-37.15(14)
N-C(1)-C(5)-C(10)	-39.38(19)
C(2)-C(1)-C(5)-C(10)	78.53(17)
N-C(1)-C(5)-C(6)	141.42(14)
C(2)-C(1)-C(5)-C(6)	-100.68(16)
C(10)-C(5)-C(6)-C(7)	1.3(2)
C(1)-C(5)-C(6)-C(7)	-179.45(14)
C(5)-C(6)-C(7)-C(8)	-0.2(2)
C(6)-C(7)-C(8)-C(9)	-0.5(2)
C(6)-C(7)-C(8)-C(11)	177.87(14)
C(7)-C(8)-C(9)-C(10)	0.0(2)
C(11)-C(8)-C(9)-C(10)	-178.27(15)
C(6)-C(5)-C(10)-C(9)	-1.8(2)
C(1)-C(5)-C(10)-C(9)	178.99(14)
C(8)-C(9)-C(10)-C(5)	1.1(2)

C(12)-O(3)-C(11)-O(4)	0.5(2)
C(12)-O(3)-C(11)-C(8)	179.37(13)
C(7)-C(8)-C(11)-O(4)	9.8(2)
C(9)-C(8)-C(11)-O(4)	-171.86(16)
C(7)-C(8)-C(11)-O(3)	-169.06(14)
C(9)-C(8)-C(11)-O(3)	9.3(2)
C(3)-C(2)-C(13)-C(14)	79.38(17)
C(1)-C(2)-C(13)-C(14)	-163.19(13)
C(2)-C(13)-C(14)-C(15)	178.82(14)
C(13)-C(14)-C(15)-C(16)	-172.72(14)
C(14)-C(15)-C(16)-C(17)	-177.44(16)
C(15)-C(16)-C(17)-C(18)	-62.6(2)
C(4)-C(3)-C(19)-C(20)	-124.01(16)
C(2)-C(3)-C(19)-C(20)	118.13(16)
C(4)-C(3)-C(19)-C(24)	58.68(19)
C(2)-C(3)-C(19)-C(24)	-59.19(19)
C(24)-C(19)-C(20)-C(21)	3.0(3)
C(3)-C(19)-C(20)-C(21)	-174.39(15)
C(19)-C(20)-C(21)-C(22)	-1.6(3)
C(20)-C(21)-C(22)-C(23)	-0.9(3)
C(20)-C(21)-C(22)-C(25)	177.13(16)
C(21)-C(22)-C(23)-C(24)	1.8(3)

C(25)-C(22)-C(23)-C(24)	-176.08(16)
C(22)-C(23)-C(24)-C(19)	-0.4(3)
C(20)-C(19)-C(24)-C(23)	-2.0(2)
C(3)-C(19)-C(24)-C(23)	175.36(15)
C(26)-O(5)-C(25)-O(6)	-1.5(3)
C(26)-O(5)-C(25)-C(22)	177.14(15)
C(21)-C(22)-C(25)-O(6)	-6.1(3)
C(23)-C(22)-C(25)-O(6)	171.86(19)
C(21)-C(22)-C(25)-O(5)	175.28(15)
C(23)-C(22)-C(25)-O(5)	-6.8(2)
O(1)-S-C(27)-C(28)	-27.01(15)
O(2)-S-C(27)-C(28)	-158.55(13)
N-S-C(27)-C(28)	86.96(14)
O(1)-S-C(27)-C(32)	158.04(13)
O(2)-S-C(27)-C(32)	26.51(15)
N-S-C(27)-C(32)	-87.99(14)
C(32)-C(27)-C(28)-C(29)	1.4(2)
S-C(27)-C(28)-C(29)	-173.50(13)
C(27)-C(28)-C(29)-C(30)	-0.7(3)
C(28)-C(29)-C(30)-C(31)	-0.6(3)
C(28)-C(29)-C(30)-C(33)	-179.15(18)
C(29)-C(30)-C(31)-C(32)	1.2(3)

C(33)-C(30)-C(31)-C(32)	179.77(18)
C(30)-C(31)-C(32)-C(27)	-0.5(3)
C(28)-C(27)-C(32)-C(31)	-0.8(2)
S-C(27)-C(32)-C(31)	174.01(13)

Symmetry transformations used to generate equivalent atoms:

The thermal ellipsoid of tetrahydro indenopyridine **4.21a** drawn at 50% probability level.

The CCDC number is 895234

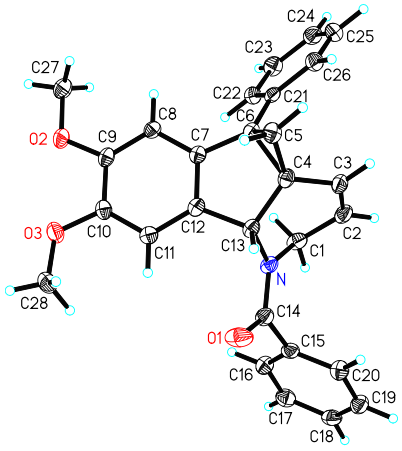


Table 1. Crystal data and structure refinement for $C_{28}H_{25}NO_3$.

Identification code	q10c
Empirical formula	$C_{28}H_{25}NO_3$

Formula weight	423.49	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.5171(3) Å	α= 90°.
	b = 9.7324(2) Å	β= 101.0310(10)°.
	c = 17.7685(4) Å	γ = 90°.
Volume	2124.59(8) $Å^3$	
Z	4	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.681 mm^{-1}	
F(000)	896	
Crystal size	0.14 x 0.05 x 0.05 mm^3	
Theta range for data collection	3.98 to 69.34°.	
Index ranges	-14<=h<=13, -11<=k<=11, -20<=l<=21	
Reflections collected	19823	
Independent reflections	3872 [R(int) = 0.0172]	
Completeness to theta = 66.00°	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.922	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3872 / 0 / 390
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0297, wR2 = 0.0738
R indices (all data)	R1 = 0.0316, wR2 = 0.0752
Extinction coefficient	0.00090(13)
Largest diff. peak and hole	0.214 and -0.180 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C28H25NO3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N	4151(1)	1092(1)	3058(1)	20(1)
O(1)	4948(1)	112(1)	2156(1)	38(1)
O(2)	-532(1)	1982(1)	1004(1)	26(1)
O(3)	1059(1)	1330(1)	357(1)	27(1)
C(1)	4137(1)	2090(1)	3680(1)	24(1)
C(2)	4186(1)	1329(1)	4421(1)	28(1)
C(3)	3564(1)	226(1)	4412(1)	26(1)
C(4)	2830(1)	-129(1)	3682(1)	21(1)
C(5)	1906(1)	-1114(1)	3650(1)	23(1)
C(6)	1631(1)	408(1)	3538(1)	19(1)
C(7)	1401(1)	796(1)	2707(1)	18(1)
C(8)	429(1)	1286(1)	2271(1)	20(1)
C(9)	357(1)	1475(1)	1489(1)	20(1)
C(10)	1239(1)	1127(1)	1133(1)	21(1)
C(11)	2202(1)	650(1)	1571(1)	20(1)
C(12)	2280(1)	517(1)	2362(1)	19(1)
C(13)	3266(1)	60(1)	2941(1)	20(1)

C(14)	4974(1)	951(1)	2676(1)	23(1)
C(15)	5961(1)	1857(1)	2900(1)	22(1)
C(16)	6026(1)	3111(1)	2537(1)	27(1)
C(17)	6979(1)	3872(1)	2691(1)	29(1)
C(18)	7878(1)	3392(1)	3204(1)	27(1)
C(19)	7812(1)	2151(1)	3574(1)	27(1)
C(20)	6856(1)	1387(1)	3428(1)	26(1)
C(21)	1244(1)	1248(1)	4135(1)	19(1)
C(22)	989(1)	2636(1)	4005(1)	23(1)
C(23)	684(1)	3444(1)	4574(1)	28(1)
C(24)	631(1)	2892(1)	5286(1)	28(1)
C(25)	876(1)	1516(1)	5418(1)	28(1)
C(26)	1178(1)	706(1)	4852(1)	24(1)
C(27)	-1426(1)	2413(1)	1336(1)	30(1)
C(28)	1823(1)	721(1)	-42(1)	30(1)

Table 3. Bond lengths [Å] and angles [°] for C28H25NO3.

N-C(14)	1.3437(14)
N-C(1)	1.4744(13)
N-C(13)	1.4805(13)

O(1)-C(14)	1.2294(13)
O(2)-C(9)	1.3627(12)
O(2)-C(27)	1.4235(14)
O(3)-C(10)	1.3676(12)
O(3)-C(28)	1.4245(14)
C(1)-C(2)	1.5010(16)
C(1)-H(1A)	0.976(14)
C(1)-H(1B)	1.004(13)
C(2)-C(3)	1.3246(17)
C(2)-H(2)	0.947(14)
C(3)-C(4)	1.4793(15)
C(3)-H(3)	0.982(14)
C(4)-C(5)	1.4954(15)
C(4)-C(13)	1.5300(14)
C(4)-C(6)	1.5638(14)
C(5)-C(6)	1.5250(14)
C(5)-H(5A)	0.986(13)
C(5)-H(5B)	0.982(13)
C(6)-C(21)	1.4912(14)
C(6)-C(7)	1.4973(14)
C(7)-C(12)	1.3846(14)
C(7)-C(8)	1.3968(14)

C(8)-C(9)	1.3860(14)
C(8)-H(8)	0.974(13)
C(9)-C(10)	1.4157(15)
C(10)-C(11)	1.3832(15)
C(11)-C(12)	1.3973(14)
C(11)-H(11)	0.969(13)
C(12)-C(13)	1.5137(14)
C(13)-H(13)	0.995(12)
C(14)-C(15)	1.5085(15)
C(15)-C(16)	1.3894(16)
C(15)-C(20)	1.3932(16)
C(16)-C(17)	1.3861(17)
C(16)-H(16)	0.980(14)
C(17)-C(18)	1.3855(17)
C(17)-H(17)	0.967(15)
C(18)-C(19)	1.3862(17)
C(18)-H(18)	0.966(14)
C(19)-C(20)	1.3905(16)
C(19)-H(19)	0.956(14)
C(20)-H(20)	0.978(14)
C(21)-C(26)	1.3954(15)
C(21)-C(22)	1.3971(15)

C(22)-C(23)	1.3910(16)
C(22)-H(22)	0.982(13)
C(23)-C(24)	1.3864(17)
C(23)-H(23)	0.981(15)
C(24)-C(25)	1.3839(17)
C(24)-H(24)	0.976(14)
C(25)-C(26)	1.3860(16)
C(25)-H(25)	0.982(15)
C(26)-H(26)	0.977(14)
C(27)-H(27A)	0.996(15)
C(27)-H(27B)	0.993(15)
C(27)-H(27C)	0.999(15)
C(28)-H(28A)	1.007(15)
C(28)-H(28B)	0.966(15)
C(28)-H(28C)	0.990(15)

C(14)-N-C(1)	124.49(9)
C(14)-N-C(13)	119.04(8)
C(1)-N-C(13)	115.82(8)
C(9)-O(2)-C(27)	117.13(8)
C(10)-O(3)-C(28)	116.45(9)
N-C(1)-C(2)	109.18(9)

N-C(1)-H(1A)	108.2(7)
C(2)-C(1)-H(1A)	112.7(8)
N-C(1)-H(1B)	107.7(7)
C(2)-C(1)-H(1B)	111.2(7)
H(1A)-C(1)-H(1B)	107.7(11)
C(3)-C(2)-C(1)	117.67(10)
C(3)-C(2)-H(2)	123.0(9)
C(1)-C(2)-H(2)	119.3(9)
C(2)-C(3)-C(4)	117.68(10)
C(2)-C(3)-H(3)	124.0(8)
C(4)-C(3)-H(3)	118.3(8)
C(3)-C(4)-C(5)	122.02(9)
C(3)-C(4)-C(13)	117.54(9)
C(5)-C(4)-C(13)	116.39(9)
C(3)-C(4)-C(6)	118.76(9)
C(5)-C(4)-C(6)	59.75(7)
C(13)-C(4)-C(6)	107.91(8)
C(4)-C(5)-C(6)	62.35(7)
C(4)-C(5)-H(5A)	116.5(7)
C(6)-C(5)-H(5A)	118.7(7)
C(4)-C(5)-H(5B)	117.8(7)
C(6)-C(5)-H(5B)	116.4(7)

H(5A)-C(5)-H(5B)	115.1(10)
C(21)-C(6)-C(7)	122.37(9)
C(21)-C(6)-C(5)	122.41(9)
C(7)-C(6)-C(5)	111.64(9)
C(21)-C(6)-C(4)	119.97(8)
C(7)-C(6)-C(4)	104.06(8)
C(5)-C(6)-C(4)	57.90(7)
C(12)-C(7)-C(8)	120.18(9)
C(12)-C(7)-C(6)	111.60(9)
C(8)-C(7)-C(6)	128.06(9)
C(9)-C(8)-C(7)	118.99(10)
C(9)-C(8)-H(8)	120.8(7)
C(7)-C(8)-H(8)	120.2(7)
O(2)-C(9)-C(8)	124.77(10)
O(2)-C(9)-C(10)	114.60(9)
C(8)-C(9)-C(10)	120.63(9)
O(3)-C(10)-C(11)	124.96(10)
O(3)-C(10)-C(9)	115.08(9)
C(11)-C(10)-C(9)	119.94(9)
C(10)-C(11)-C(12)	118.88(10)
C(10)-C(11)-H(11)	120.5(7)
C(12)-C(11)-H(11)	120.6(7)

C(7)-C(12)-C(11)	121.26(9)
C(7)-C(12)-C(13)	111.72(9)
C(11)-C(12)-C(13)	127.01(9)
N-C(13)-C(12)	112.79(8)
N-C(13)-C(4)	109.99(8)
C(12)-C(13)-C(4)	103.99(8)
N-C(13)-H(13)	105.8(7)
C(12)-C(13)-H(13)	112.8(7)
C(4)-C(13)-H(13)	111.6(7)
O(1)-C(14)-N	122.35(10)
O(1)-C(14)-C(15)	119.25(9)
N-C(14)-C(15)	118.40(9)
C(16)-C(15)-C(20)	119.33(10)
C(16)-C(15)-C(14)	120.61(10)
C(20)-C(15)-C(14)	119.84(10)
C(17)-C(16)-C(15)	120.14(11)
C(17)-C(16)-H(16)	119.7(8)
C(15)-C(16)-H(16)	120.1(8)
C(18)-C(17)-C(16)	120.62(11)
C(18)-C(17)-H(17)	119.4(9)
C(16)-C(17)-H(17)	120.0(9)
C(17)-C(18)-C(19)	119.45(10)

C(17)-C(18)-H(18)	120.1(8)
C(19)-C(18)-H(18)	120.5(8)
C(18)-C(19)-C(20)	120.25(11)
C(18)-C(19)-H(19)	119.4(8)
C(20)-C(19)-H(19)	120.3(8)
C(19)-C(20)-C(15)	120.19(11)
C(19)-C(20)-H(20)	119.8(8)
C(15)-C(20)-H(20)	120.0(8)
C(26)-C(21)-C(22)	117.67(10)
C(26)-C(21)-C(6)	121.75(9)
C(22)-C(21)-C(6)	120.50(9)
C(23)-C(22)-C(21)	120.81(10)
C(23)-C(22)-H(22)	119.6(8)
C(21)-C(22)-H(22)	119.6(8)
C(24)-C(23)-C(22)	120.78(11)
C(24)-C(23)-H(23)	121.0(8)
C(22)-C(23)-H(23)	118.2(8)
C(25)-C(24)-C(23)	118.82(11)
C(25)-C(24)-H(24)	119.5(8)
C(23)-C(24)-H(24)	121.6(8)
C(24)-C(25)-C(26)	120.59(11)
C(24)-C(25)-H(25)	119.4(8)

C(26)-C(25)-H(25)	120.0(8)
C(25)-C(26)-C(21)	121.33(10)
C(25)-C(26)-H(26)	118.3(8)
C(21)-C(26)-H(26)	120.4(8)
O(2)-C(27)-H(27A)	111.2(8)
O(2)-C(27)-H(27B)	104.4(8)
H(27A)-C(27)-H(27B)	110.3(11)
O(2)-C(27)-H(27C)	110.8(8)
H(27A)-C(27)-H(27C)	108.7(11)
H(27B)-C(27)-H(27C)	111.5(12)
O(3)-C(28)-H(28A)	111.1(8)
O(3)-C(28)-H(28B)	104.9(8)
H(28A)-C(28)-H(28B)	109.9(11)
O(3)-C(28)-H(28C)	110.9(8)
H(28A)-C(28)-H(28C)	109.0(11)
H(28B)-C(28)-H(28C)	111.0(12)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C28H25NO3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N	16(1)	21(1)	22(1)	-6(1)	2(1)	0(1)
O(1)	31(1)	44(1)	43(1)	-25(1)	16(1)	-10(1)
O(2)	22(1)	32(1)	22(1)	4(1)	-1(1)	7(1)
O(3)	31(1)	33(1)	18(1)	1(1)	3(1)	6(1)
C(1)	19(1)	25(1)	30(1)	-11(1)	5(1)	-1(1)
C(2)	18(1)	40(1)	23(1)	-11(1)	0(1)	4(1)
C(3)	20(1)	35(1)	21(1)	1(1)	1(1)	7(1)
C(4)	19(1)	19(1)	22(1)	1(1)	1(1)	4(1)
C(5)	25(1)	18(1)	24(1)	3(1)	3(1)	2(1)
C(6)	16(1)	18(1)	21(1)	2(1)	1(1)	0(1)
C(7)	19(1)	14(1)	20(1)	-1(1)	2(1)	-2(1)
C(8)	18(1)	18(1)	22(1)	0(1)	3(1)	0(1)
C(9)	20(1)	18(1)	22(1)	1(1)	-1(1)	0(1)
C(10)	25(1)	18(1)	18(1)	0(1)	2(1)	-2(1)
C(11)	20(1)	17(1)	22(1)	-3(1)	4(1)	-1(1)
C(12)	19(1)	14(1)	22(1)	-2(1)	1(1)	-1(1)
C(13)	18(1)	18(1)	22(1)	-3(1)	1(1)	1(1)
C(14)	20(1)	24(1)	24(1)	-5(1)	3(1)	1(1)
C(15)	20(1)	25(1)	21(1)	-6(1)	6(1)	1(1)
C(16)	24(1)	30(1)	27(1)	1(1)	3(1)	3(1)

C(17)	31(1)	27(1)	29(1)	2(1)	10(1)	-2(1)
C(18)	22(1)	31(1)	28(1)	-6(1)	10(1)	-6(1)
C(19)	22(1)	31(1)	26(1)	-3(1)	2(1)	0(1)
C(20)	26(1)	24(1)	26(1)	-1(1)	3(1)	-1(1)
C(21)	13(1)	23(1)	21(1)	0(1)	1(1)	-2(1)
C(22)	22(1)	24(1)	23(1)	2(1)	4(1)	0(1)
C(23)	27(1)	25(1)	31(1)	-2(1)	4(1)	4(1)
C(24)	23(1)	35(1)	26(1)	-7(1)	5(1)	2(1)
C(25)	27(1)	37(1)	22(1)	2(1)	5(1)	-2(1)
C(26)	24(1)	25(1)	24(1)	3(1)	4(1)	0(1)
C(27)	22(1)	35(1)	30(1)	5(1)	1(1)	9(1)
C(28)	33(1)	36(1)	21(1)	-3(1)	6(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C28H25NO3.

	x	y	z	U(eq)
H(1A)	4747(11)	2720(14)	3695(7)	27(3)
H(1B)	3448(11)	2639(13)	3544(7)	26(3)

H(2)	4653(11)	1650(15)	4869(8)	35(4)
H(3)	3546(11)	-351(14)	4863(8)	32(3)
H(5A)	1832(10)	-1555(13)	4137(7)	24(3)
H(5B)	1716(10)	-1700(13)	3193(7)	24(3)
H(8)	-186(10)	1496(13)	2514(7)	22(3)
H(11)	2815(10)	426(12)	1333(7)	21(3)
H(13)	3594(10)	-801(13)	2788(7)	20(3)
H(16)	5399(12)	3459(14)	2169(8)	33(3)
H(17)	7020(12)	4748(16)	2441(8)	38(4)
H(18)	8546(12)	3916(14)	3296(8)	33(3)
H(19)	8431(11)	1823(14)	3930(8)	29(3)
H(20)	6816(11)	512(15)	3691(8)	32(3)
H(22)	1027(10)	3046(13)	3506(7)	27(3)
H(23)	511(11)	4414(16)	4459(8)	36(4)
H(24)	441(11)	3454(14)	5696(8)	34(3)
H(25)	831(11)	1113(15)	5918(8)	37(4)
H(26)	1348(11)	-260(14)	4967(7)	29(3)
H(27A)	-1759(11)	1621(15)	1561(8)	35(4)
H(27B)	-1953(12)	2809(15)	900(8)	38(4)
H(27C)	-1188(12)	3110(15)	1747(8)	36(4)
H(28A)	2558(12)	1175(15)	100(8)	35(4)
H(28B)	1525(12)	877(15)	-578(8)	37(4)

H(28C)	1903(11)	-273(16)	71(8)	36(4)

Table 6. Torsion angles [°] for C28H25NO3.

C(14)-N-C(1)-C(2)	-112.61(11)
C(13)-N-C(1)-C(2)	57.96(11)
N-C(1)-C(2)-C(3)	-43.76(13)
C(1)-C(2)-C(3)-C(4)	-3.05(15)
C(2)-C(3)-C(4)-C(5)	-164.16(10)
C(2)-C(3)-C(4)-C(13)	39.29(14)
C(2)-C(3)-C(4)-C(6)	-93.70(12)
C(3)-C(4)-C(5)-C(6)	107.00(11)
C(13)-C(4)-C(5)-C(6)	-96.21(9)
C(4)-C(5)-C(6)-C(21)	-107.47(10)
C(4)-C(5)-C(6)-C(7)	93.42(9)
C(3)-C(4)-C(6)-C(21)	-0.71(14)
C(5)-C(4)-C(6)-C(21)	111.63(10)
C(13)-C(4)-C(6)-C(21)	-137.74(9)
C(3)-C(4)-C(6)-C(7)	140.70(10)
C(5)-C(4)-C(6)-C(7)	-106.96(9)
C(13)-C(4)-C(6)-C(7)	3.66(10)

C(3)-C(4)-C(6)-C(5)	-112.34(11)
C(13)-C(4)-C(6)-C(5)	110.63(9)
C(21)-C(6)-C(7)-C(12)	142.06(9)
C(5)-C(6)-C(7)-C(12)	-58.82(11)
C(4)-C(6)-C(7)-C(12)	1.83(11)
C(21)-C(6)-C(7)-C(8)	-42.58(15)
C(5)-C(6)-C(7)-C(8)	116.54(11)
C(4)-C(6)-C(7)-C(8)	177.20(10)
C(12)-C(7)-C(8)-C(9)	0.54(15)
C(6)-C(7)-C(8)-C(9)	-174.47(10)
C(27)-O(2)-C(9)-C(8)	3.45(15)
C(27)-O(2)-C(9)-C(10)	-177.01(9)
C(7)-C(8)-C(9)-O(2)	-178.04(9)
C(7)-C(8)-C(9)-C(10)	2.45(15)
C(28)-O(3)-C(10)-C(11)	14.65(15)
C(28)-O(3)-C(10)-C(9)	-166.78(10)
O(2)-C(9)-C(10)-O(3)	-1.05(13)
C(8)-C(9)-C(10)-O(3)	178.52(9)
O(2)-C(9)-C(10)-C(11)	177.59(9)
C(8)-C(9)-C(10)-C(11)	-2.84(15)
O(3)-C(10)-C(11)-C(12)	178.71(9)
C(9)-C(10)-C(11)-C(12)	0.21(15)

C(8)-C(7)-C(12)-C(11)	-3.21(15)
C(6)-C(7)-C(12)-C(11)	172.57(9)
C(8)-C(7)-C(12)-C(13)	177.38(9)
C(6)-C(7)-C(12)-C(13)	-6.84(12)
C(10)-C(11)-C(12)-C(7)	2.80(15)
C(10)-C(11)-C(12)-C(13)	-177.89(9)
C(14)-N-C(13)-C(12)	-97.35(11)
C(1)-N-C(13)-C(12)	91.54(11)
C(14)-N-C(13)-C(4)	147.06(9)
C(1)-N-C(13)-C(4)	-24.05(12)
C(7)-C(12)-C(13)-N	-110.37(10)
C(11)-C(12)-C(13)-N	70.26(13)
C(7)-C(12)-C(13)-C(4)	8.76(11)
C(11)-C(12)-C(13)-C(4)	-170.61(10)
C(3)-C(4)-C(13)-N	-23.87(12)
C(5)-C(4)-C(13)-N	178.26(8)
C(6)-C(4)-C(13)-N	113.77(9)
C(3)-C(4)-C(13)-C(12)	-144.89(9)
C(5)-C(4)-C(13)-C(12)	57.24(11)
C(6)-C(4)-C(13)-C(12)	-7.26(10)
C(1)-N-C(14)-O(1)	-179.37(11)
C(13)-N-C(14)-O(1)	10.34(16)

C(1)-N-C(14)-C(15)	0.73(15)
C(13)-N-C(14)-C(15)	-169.56(9)
O(1)-C(14)-C(15)-C(16)	88.56(14)
N-C(14)-C(15)-C(16)	-91.54(13)
O(1)-C(14)-C(15)-C(20)	-85.97(14)
N-C(14)-C(15)-C(20)	93.93(12)
C(20)-C(15)-C(16)-C(17)	1.10(16)
C(14)-C(15)-C(16)-C(17)	-173.46(10)
C(15)-C(16)-C(17)-C(18)	0.25(17)
C(16)-C(17)-C(18)-C(19)	-1.11(17)
C(17)-C(18)-C(19)-C(20)	0.61(17)
C(18)-C(19)-C(20)-C(15)	0.74(17)
C(16)-C(15)-C(20)-C(19)	-1.59(16)
C(14)-C(15)-C(20)-C(19)	173.01(10)
C(7)-C(6)-C(21)-C(26)	161.17(10)
C(5)-C(6)-C(21)-C(26)	4.28(15)
C(4)-C(6)-C(21)-C(26)	-64.59(13)
C(7)-C(6)-C(21)-C(22)	-22.32(14)
C(5)-C(6)-C(21)-C(22)	-179.22(9)
C(4)-C(6)-C(21)-C(22)	111.92(11)
C(26)-C(21)-C(22)-C(23)	0.18(15)
C(6)-C(21)-C(22)-C(23)	-176.47(10)

C(21)-C(22)-C(23)-C(24)	0.33(17)
C(22)-C(23)-C(24)-C(25)	-0.66(17)
C(23)-C(24)-C(25)-C(26)	0.50(17)
C(24)-C(25)-C(26)-C(21)	0.00(17)
C(22)-C(21)-C(26)-C(25)	-0.34(16)
C(6)-C(21)-C(26)-C(25)	176.26(10)

Symmetry transformations used to generate equivalent atoms:

The thermal ellipsoid of tetrahydro indenopyridine **4.20** drawn at 50% probability level. The CCDC number is 900884.

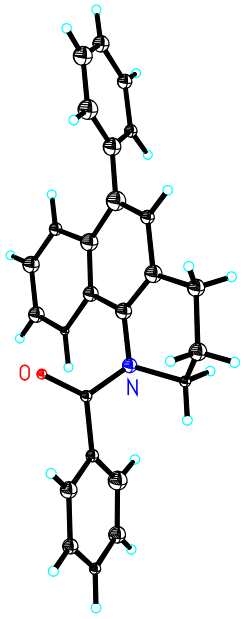


Table 1. Crystal data and structure refinement for $C_{26}H_{21}NO$.

Identification code	q01a	
Empirical formula	$C_{26}H_{21}NO$	
Formula weight	363.44	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.7537(3) Å	α= 74.1310(10)°.
	b = 9.8726(3) Å	β= 81.6140(10)°.
	c = 11.2156(3) Å	γ = 61.630(2)°.
Volume	913.91(5) $Å^3$	

Z	2
Density (calculated)	1.321 Mg/m^3
Absorption coefficient	0.619 mm^{-1}
F(000)	384
Crystal size	0.26 x 0.14 x 0.08 mm^3
Theta range for data collection	4.10 to 69.22°.
Index ranges	-11<=h<=11, -11<=k<=11, -13<=l<=13
Reflections collected	7593
Independent reflections	2954 [R(int) = 0.0330]
Completeness to theta = 66.00°	90.4 %
Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.807
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2954 / 0 / 309
Goodness-of-fit on F^2	1.135
Final R indices [I>2sigma(I)]	R1 = 0.0592, wR2 = 0.1776
R indices (all data)	R1 = 0.0666, wR2 = 0.1828
Largest diff. peak and hole	0.427 and -0.375 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C26H21NO. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O	4793(2)	3339(2)	41(1)	23(1)
N	2151(2)	4739(2)	286(2)	20(1)
C(1)	954(3)	6411(3)	69(2)	24(1)
C(2)	1257(3)	7212(3)	907(2)	25(1)
C(3)	1148(3)	6406(3)	2266(2)	24(1)
C(4)	1717(2)	4640(3)	2491(2)	20(1)
C(5)	2180(2)	3872(3)	1542(2)	20(1)
C(6)	2579(2)	2222(3)	1781(2)	19(1)
C(7)	2971(2)	1406(3)	821(2)	21(1)
C(8)	3355(3)	-165(3)	1081(2)	24(1)
C(9)	3392(3)	-1021(3)	2316(2)	24(1)
C(10)	2990(3)	-264(3)	3263(2)	22(1)
C(11)	2554(2)	1373(3)	3031(2)	20(1)
C(12)	2121(2)	2179(3)	4011(2)	21(1)
C(13)	1718(3)	3765(3)	3720(2)	21(1)
C(14)	2110(3)	1320(3)	5332(2)	21(1)
C(15)	3188(3)	1079(3)	6155(2)	28(1)

C(16)	3218(3)	239(3)	7376(2)	31(1)
C(17)	2170(3)	-371(3)	7791(2)	27(1)
C(18)	1068(3)	-114(3)	6991(2)	24(1)
C(19)	1038(3)	726(3)	5770(2)	23(1)
C(20)	3533(2)	4333(3)	-408(2)	19(1)
C(21)	3380(3)	5080(3)	-1768(2)	20(1)
C(22)	4456(3)	5596(3)	-2374(2)	23(1)
C(23)	4406(3)	6174(3)	-3649(2)	25(1)
C(24)	3286(3)	6219(3)	-4324(2)	25(1)
C(25)	2214(3)	5715(3)	-3724(2)	27(1)
C(26)	2243(3)	5160(3)	-2448(2)	25(1)

Table 3. Bond lengths [Å] and angles [°] for C26H21NO.

O-C(20)	1.221(3)
N-C(20)	1.391(3)
N-C(5)	1.431(3)
N-C(1)	1.476(3)
C(1)-C(2)	1.519(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.529(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.513(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.374(3)
C(4)-C(13)	1.412(3)
C(5)-C(6)	1.438(3)
C(6)-C(7)	1.420(3)
C(6)-C(11)	1.426(3)
C(7)-C(8)	1.365(3)
C(7)-H(7)	0.98(2)

C(8)-C(9)	1.407(3)
C(8)-H(8)	0.97(3)
C(9)-C(10)	1.369(3)
C(9)-H(9)	0.94(3)
C(10)-C(11)	1.418(3)
C(10)-H(10)	0.99(3)
C(11)-C(12)	1.429(3)
C(12)-C(13)	1.373(3)
C(12)-C(14)	1.494(3)
C(13)-H(4)	0.98(3)
C(14)-C(15)	1.393(3)
C(14)-C(19)	1.398(3)
C(15)-C(16)	1.389(3)
C(15)-H(15)	0.99(3)
C(16)-C(17)	1.385(4)
C(16)-H(16)	0.97(3)
C(17)-C(18)	1.386(3)
C(17)-H(17)	0.96(3)
C(18)-C(19)	1.390(3)
C(18)-H(18)	0.91(3)
C(19)-H(19)	0.99(3)
C(20)-C(21)	1.497(3)

C(21)-C(22)	1.391(3)
C(21)-C(26)	1.395(3)
C(22)-C(23)	1.386(3)
C(22)-H(22)	1.00(3)
C(23)-C(24)	1.395(3)
C(23)-H(23)	0.97(3)
C(24)-C(25)	1.378(3)
C(24)-H(24)	0.97(3)
C(25)-C(26)	1.385(3)
C(25)-H(25)	0.9500
C(26)-H(26)	0.98(3)

C(20)-N-C(5)	119.04(18)
C(20)-N-C(1)	119.35(19)
C(5)-N-C(1)	113.47(18)
N-C(1)-C(2)	108.87(18)
N-C(1)-H(1A)	109.9
C(2)-C(1)-H(1A)	109.9
N-C(1)-H(1B)	109.9
C(2)-C(1)-H(1B)	109.9
H(1A)-C(1)-H(1B)	108.3
C(1)-C(2)-C(3)	110.1(2)

C(1)-C(2)-H(2A)	109.6
C(3)-C(2)-H(2A)	109.6
C(1)-C(2)-H(2B)	109.6
C(3)-C(2)-H(2B)	109.6
H(2A)-C(2)-H(2B)	108.2
C(4)-C(3)-C(2)	113.69(19)
C(4)-C(3)-H(3A)	108.8
C(2)-C(3)-H(3A)	108.8
C(4)-C(3)-H(3B)	108.8
C(2)-C(3)-H(3B)	108.8
H(3A)-C(3)-H(3B)	107.7
C(5)-C(4)-C(13)	119.0(2)
C(5)-C(4)-C(3)	122.4(2)
C(13)-C(4)-C(3)	118.5(2)
C(4)-C(5)-N	120.1(2)
C(4)-C(5)-C(6)	120.8(2)
N-C(5)-C(6)	118.9(2)
C(7)-C(6)-C(11)	118.5(2)
C(7)-C(6)-C(5)	122.7(2)
C(11)-C(6)-C(5)	118.8(2)
C(8)-C(7)-C(6)	121.2(2)
C(8)-C(7)-H(7)	119.7(15)

C(6)-C(7)-H(7)	119.1(15)
C(7)-C(8)-C(9)	120.5(2)
C(7)-C(8)-H(8)	119.2(16)
C(9)-C(8)-H(8)	120.3(16)
C(10)-C(9)-C(8)	119.9(2)
C(10)-C(9)-H(9)	120.1(18)
C(8)-C(9)-H(9)	120.1(18)
C(9)-C(10)-C(11)	121.4(2)
C(9)-C(10)-H(10)	121.1(16)
C(11)-C(10)-H(10)	117.4(16)
C(10)-C(11)-C(6)	118.5(2)
C(10)-C(11)-C(12)	122.0(2)
C(6)-C(11)-C(12)	119.6(2)
C(13)-C(12)-C(11)	118.9(2)
C(13)-C(12)-C(14)	120.2(2)
C(11)-C(12)-C(14)	121.0(2)
C(12)-C(13)-C(4)	122.9(2)
C(12)-C(13)-H(4)	118.0(15)
C(4)-C(13)-H(4)	119.1(15)
C(15)-C(14)-C(19)	118.4(2)
C(15)-C(14)-C(12)	120.3(2)
C(19)-C(14)-C(12)	121.26(19)

C(16)-C(15)-C(14)	120.8(2)
C(16)-C(15)-H(15)	121.5(14)
C(14)-C(15)-H(15)	117.6(14)
C(17)-C(16)-C(15)	120.2(2)
C(17)-C(16)-H(16)	121.0(18)
C(15)-C(16)-H(16)	118.8(18)
C(16)-C(17)-C(18)	119.8(2)
C(16)-C(17)-H(17)	119.7(17)
C(18)-C(17)-H(17)	120.5(17)
C(17)-C(18)-C(19)	120.0(2)
C(17)-C(18)-H(18)	120.9(17)
C(19)-C(18)-H(18)	119.1(17)
C(18)-C(19)-C(14)	120.8(2)
C(18)-C(19)-H(19)	121.7(19)
C(14)-C(19)-H(19)	117.5(18)
O-C(20)-N	122.38(19)
O-C(20)-C(21)	121.24(19)
N-C(20)-C(21)	116.18(18)
C(22)-C(21)-C(26)	119.7(2)
C(22)-C(21)-C(20)	119.35(19)
C(26)-C(21)-C(20)	120.8(2)
C(23)-C(22)-C(21)	120.1(2)

C(23)-C(22)-H(22)	122.0(18)
C(21)-C(22)-H(22)	117.9(18)
C(22)-C(23)-C(24)	119.8(2)
C(22)-C(23)-H(23)	121.1(17)
C(24)-C(23)-H(23)	119.1(17)
C(25)-C(24)-C(23)	120.2(2)
C(25)-C(24)-H(24)	120.8(17)
C(23)-C(24)-H(24)	119.0(17)
C(24)-C(25)-C(26)	120.2(2)
C(24)-C(25)-H(25)	119.9
C(26)-C(25)-H(25)	119.9
C(25)-C(26)-C(21)	120.0(2)
C(25)-C(26)-H(26)	121.1(16)
C(21)-C(26)-H(26)	118.9(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C26H21NO. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

O	21(1)	23(1)	22(1)	-5(1)	-4(1)	-9(1)
N	20(1)	21(1)	17(1)	-4(1)	-3(1)	-7(1)
C(1)	19(1)	25(1)	22(1)	-4(1)	-3(1)	-7(1)
C(2)	26(1)	19(1)	26(1)	-5(1)	-1(1)	-8(1)
C(3)	26(1)	24(1)	23(1)	-10(1)	0(1)	-10(1)
C(4)	17(1)	24(1)	21(1)	-5(1)	-3(1)	-10(1)
C(5)	17(1)	25(1)	19(1)	-4(1)	-4(1)	-9(1)
C(6)	15(1)	23(1)	21(1)	-5(1)	-5(1)	-8(1)
C(7)	18(1)	25(1)	20(1)	-5(1)	-4(1)	-8(1)
C(8)	20(1)	28(1)	25(1)	-10(1)	-3(1)	-11(1)
C(9)	23(1)	19(1)	31(1)	-7(1)	-3(1)	-10(1)
C(10)	21(1)	23(1)	22(1)	-3(1)	-3(1)	-10(1)
C(11)	15(1)	23(1)	22(1)	-4(1)	-4(1)	-8(1)
C(12)	18(1)	26(1)	21(1)	-6(1)	-5(1)	-10(1)
C(13)	21(1)	26(1)	20(1)	-9(1)	-2(1)	-12(1)
C(14)	20(1)	22(1)	20(1)	-7(1)	-3(1)	-7(1)
C(15)	25(1)	37(2)	23(1)	-4(1)	-4(1)	-15(1)
C(16)	25(1)	44(2)	21(1)	-2(1)	-8(1)	-14(1)
C(17)	29(1)	25(1)	20(1)	-3(1)	-2(1)	-8(1)
C(18)	27(1)	24(1)	25(1)	-7(1)	0(1)	-14(1)
C(19)	26(1)	24(1)	22(1)	-7(1)	-4(1)	-12(1)
C(20)	22(1)	19(1)	20(1)	-7(1)	-2(1)	-10(1)

C(21)	21(1)	18(1)	19(1)	-7(1)	-2(1)	-5(1)
C(22)	23(1)	22(1)	24(1)	-7(1)	-3(1)	-9(1)
C(23)	28(1)	25(1)	23(1)	-6(1)	2(1)	-12(1)
C(24)	31(1)	23(1)	18(1)	-6(1)	-1(1)	-9(1)
C(25)	28(1)	32(2)	23(1)	-10(1)	-6(1)	-12(1)
C(26)	26(1)	31(2)	22(1)	-7(1)	-1(1)	-15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C26H21NO.

	x	y	z	U(eq)
H(1A)	-95	6471	250	28
H(1B)	996	6953	-810	28
H(2A)	482	8344	750	30
H(2B)	2307	7149	723	30
H(3A)	1769	6592	2768	29
H(3B)	49	6902	2555	29
H(7)	2980(30)	1980(30)	-40(20)	17(6)
H(8)	3640(30)	-690(30)	410(30)	24(7)

H(9)	3690(30)	-2110(40)	2490(30)	34(8)
H(10)	3010(30)	-840(30)	4140(30)	27(7)
H(4)	1400(30)	4310(30)	4400(20)	21(6)
H(15)	3960(30)	1470(30)	5830(20)	21(6)
H(16)	3990(30)	80(40)	7930(30)	37(8)
H(17)	2180(30)	-930(40)	8640(30)	34(7)
H(18)	380(30)	-520(30)	7250(20)	28(7)
H(19)	270(40)	920(40)	5180(30)	42(8)
H(22)	5220(40)	5580(40)	-1860(30)	41(8)
H(23)	5120(30)	6580(40)	-4080(30)	35(8)
H(24)	3290(30)	6590(30)	-5220(30)	31(7)
H(25)	1453	5749	-4188	33
H(26)	1500(30)	4790(30)	-2010(20)	26(7)

Table 6. Torsion angles [°] for C26H21NO.

C(20)-N-C(1)-C(2)	-89.5(2)
C(5)-N-C(1)-C(2)	58.8(2)
N-C(1)-C(2)-C(3)	-61.1(2)
C(1)-C(2)-C(3)-C(4)	34.2(3)
C(2)-C(3)-C(4)-C(5)	-4.3(3)

C(2)-C(3)-C(4)-C(13)	177.94(19)
C(13)-C(4)-C(5)-N	178.32(18)
C(3)-C(4)-C(5)-N	0.6(3)
C(13)-C(4)-C(5)-C(6)	3.4(3)
C(3)-C(4)-C(5)-C(6)	-174.30(18)
C(20)-N-C(5)-C(4)	120.0(2)
C(1)-N-C(5)-C(4)	-28.5(3)
C(20)-N-C(5)-C(6)	-65.0(3)
C(1)-N-C(5)-C(6)	146.50(19)
C(4)-C(5)-C(6)-C(7)	176.05(19)
N-C(5)-C(6)-C(7)	1.1(3)
C(4)-C(5)-C(6)-C(11)	-2.8(3)
N-C(5)-C(6)-C(11)	-177.78(18)
C(11)-C(6)-C(7)-C(8)	-1.6(3)
C(5)-C(6)-C(7)-C(8)	179.53(19)
C(6)-C(7)-C(8)-C(9)	-0.9(3)
C(7)-C(8)-C(9)-C(10)	2.2(3)
C(8)-C(9)-C(10)-C(11)	-0.9(3)
C(9)-C(10)-C(11)-C(6)	-1.6(3)
C(9)-C(10)-C(11)-C(12)	179.5(2)
C(7)-C(6)-C(11)-C(10)	2.8(3)
C(5)-C(6)-C(11)-C(10)	-178.25(18)

C(7)-C(6)-C(11)-C(12)	-178.31(18)
C(5)-C(6)-C(11)-C(12)	0.6(3)
C(10)-C(11)-C(12)-C(13)	179.73(19)
C(6)-C(11)-C(12)-C(13)	0.9(3)
C(10)-C(11)-C(12)-C(14)	-0.1(3)
C(6)-C(11)-C(12)-C(14)	-178.91(18)
C(11)-C(12)-C(13)-C(4)	-0.3(3)
C(14)-C(12)-C(13)-C(4)	179.51(19)
C(5)-C(4)-C(13)-C(12)	-1.9(3)
C(3)-C(4)-C(13)-C(12)	175.93(19)
C(13)-C(12)-C(14)-C(15)	-67.9(3)
C(11)-C(12)-C(14)-C(15)	112.0(3)
C(13)-C(12)-C(14)-C(19)	112.8(3)
C(11)-C(12)-C(14)-C(19)	-67.4(3)
C(19)-C(14)-C(15)-C(16)	1.3(4)
C(12)-C(14)-C(15)-C(16)	-178.0(2)
C(14)-C(15)-C(16)-C(17)	0.0(4)
C(15)-C(16)-C(17)-C(18)	-1.3(4)
C(16)-C(17)-C(18)-C(19)	1.3(4)
C(17)-C(18)-C(19)-C(14)	0.0(4)
C(15)-C(14)-C(19)-C(18)	-1.3(4)
C(12)-C(14)-C(19)-C(18)	178.0(2)

C(5)-N-C(20)-O	-5.5(3)
C(1)-N-C(20)-O	141.1(2)
C(5)-N-C(20)-C(21)	169.4(2)
C(1)-N-C(20)-C(21)	-44.0(3)
O-C(20)-C(21)-C(22)	-44.9(3)
N-C(20)-C(21)-C(22)	140.1(2)
O-C(20)-C(21)-C(26)	130.4(2)
N-C(20)-C(21)-C(26)	-44.6(3)
C(26)-C(21)-C(22)-C(23)	-0.5(4)
C(20)-C(21)-C(22)-C(23)	174.9(2)
C(21)-C(22)-C(23)-C(24)	-0.8(4)
C(22)-C(23)-C(24)-C(25)	1.1(4)
C(23)-C(24)-C(25)-C(26)	-0.1(4)
C(24)-C(25)-C(26)-C(21)	-1.3(4)
C(22)-C(21)-C(26)-C(25)	1.6(4)
C(20)-C(21)-C(26)-C(25)	-173.8(2)

Symmetry transformations used to generate equivalent atoms:

The thermal ellipsoid of tetrahydro indenopyridine **4.22a** drawn at 50% probability level. The CCDC number is 895235

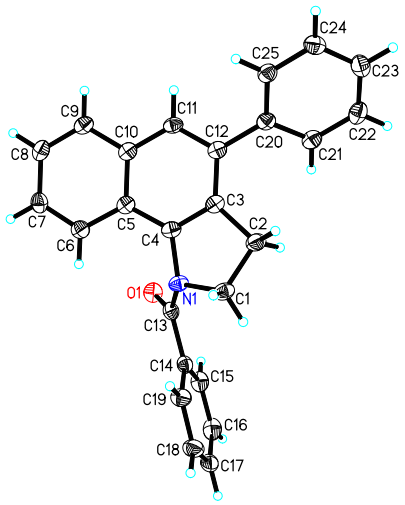


Table 1. Crystal data and structure refinement for $C_{25}H_{19}NO$.

Identification code	v63a	
Empirical formula	$C_{25}H_{19}NO$	
Formula weight	349.41	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 23.8895(15) Å	α= 90°.
	b = 9.8805(6) Å	β= 90°.
	c = 30.8596(19) Å	γ = 90°.
Volume	7284.1(8) $Å^3$	

Z	16
Density (calculated)	1.274 Mg/m^3
Absorption coefficient	0.601 mm^{-1}
F(000)	2944
Crystal size	0.15 x 0.06 x 0.01 mm^3
Theta range for data collection	2.86 to 67.66°.
Index ranges	-21<=h<=28, -11<=k<=11, -36<=l<=37
Reflections collected	62045
Independent reflections	6473 [R(int) = 0.0393]
Completeness to theta = 67.66°	98.4 %
Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.804
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6473 / 0 / 487
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0794
R indices (all data)	R1 = 0.0374, wR2 = 0.0842
Largest diff. peak and hole	0.209 and -0.208 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C25H19NO. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2849(1)	1961(1)	-7(1)	26(1)
N(1)	2526(1)	3713(1)	396(1)	22(1)
C(1)	2035(1)	4206(1)	649(1)	25(1)
C(2)	2123(1)	3581(1)	1098(1)	28(1)
C(3)	2752(1)	3422(1)	1116(1)	22(1)
C(4)	2968(1)	3538(1)	707(1)	21(1)
C(5)	3551(1)	3549(1)	619(1)	21(1)
C(6)	3791(1)	3755(1)	204(1)	24(1)
C(7)	4359(1)	3796(1)	155(1)	26(1)
C(8)	4716(1)	3630(1)	516(1)	26(1)
C(9)	4497(1)	3425(1)	920(1)	24(1)
C(10)	3909(1)	3385(1)	985(1)	21(1)
C(11)	3677(1)	3211(1)	1404(1)	22(1)
C(12)	3109(1)	3218(1)	1478(1)	22(1)
C(13)	2483(1)	2801(1)	61(1)	21(1)
C(14)	1980(1)	2872(1)	-227(1)	21(1)
C(15)	1797(1)	1654(1)	-405(1)	27(1)
C(16)	1339(1)	1636(1)	-679(1)	31(1)
C(17)	1072(1)	2831(1)	-787(1)	31(1)
C(18)	1261(1)	4046(1)	-619(1)	31(1)

C(19)	1713(1)	4074(1)	-335(1)	26(1)
C(20)	2875(1)	3021(1)	1920(1)	22(1)
C(21)	2414(1)	2180(1)	1991(1)	26(1)
C(22)	2195(1)	2017(1)	2403(1)	29(1)
C(23)	2433(1)	2677(1)	2753(1)	29(1)
C(24)	2897(1)	3491(1)	2690(1)	28(1)
C(25)	3116(1)	3661(1)	2277(1)	24(1)
O(31)	5481(1)	3885(1)	1673(1)	24(1)
N(31)	6097(1)	4213(1)	2227(1)	21(1)
C(31)	6350(1)	5237(1)	2521(1)	23(1)
C(32)	6019(1)	5051(1)	2943(1)	21(1)
C(33)	5842(1)	3580(1)	2918(1)	19(1)
C(34)	5886(1)	3152(1)	2495(1)	19(1)
C(35)	5781(1)	1800(1)	2364(1)	20(1)
C(36)	5903(1)	1265(1)	1946(1)	23(1)
C(37)	5799(1)	-67(1)	1855(1)	26(1)
C(38)	5562(1)	-930(1)	2170(1)	26(1)
C(39)	5454(1)	-456(1)	2577(1)	23(1)
C(40)	5578(1)	909(1)	2691(1)	20(1)
C(41)	5527(1)	1370(1)	3124(1)	20(1)
C(42)	5661(1)	2677(1)	3248(1)	19(1)
C(43)	5876(1)	4512(1)	1827(1)	21(1)

C(44)	6161(1)	5586(1)	1565(1)	23(1)
C(45)	5835(1)	6345(1)	1281(1)	26(1)
C(46)	6084(1)	7225(1)	990(1)	32(1)
C(47)	6663(1)	7331(1)	973(1)	35(1)
C(48)	6989(1)	6568(1)	1251(1)	34(1)
C(49)	6740(1)	5709(1)	1552(1)	28(1)
C(50)	5603(1)	3087(1)	3711(1)	20(1)
C(51)	5406(1)	4366(1)	3830(1)	24(1)
C(52)	5330(1)	4702(1)	4264(1)	27(1)
C(53)	5446(1)	3764(1)	4586(1)	28(1)
C(54)	5645(1)	2494(1)	4474(1)	27(1)
C(55)	5724(1)	2158(1)	4041(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for C25H19NO.

O(1)-C(13)	1.2248(14)
N(1)-C(13)	1.3757(15)
N(1)-C(4)	1.4366(15)
N(1)-C(1)	1.4885(15)
C(1)-C(2)	1.5339(17)
C(1)-H(1A)	0.9900

C(1)-H(1B)	0.9900
C(2)-C(3)	1.5111(16)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.3706(17)
C(3)-C(12)	1.4194(17)
C(4)-C(5)	1.4168(17)
C(5)-C(6)	1.4175(17)
C(5)-C(10)	1.4265(17)
C(6)-C(7)	1.3656(18)
C(6)-H(6A)	0.9500
C(7)-C(8)	1.4114(18)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.3685(18)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.4193(16)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.4180(17)
C(11)-C(12)	1.3775(17)
C(11)-H(11A)	0.9500
C(12)-C(20)	1.4857(16)
C(13)-C(14)	1.4954(16)

C(14)-C(19)	1.3900(17)
C(14)-C(15)	1.3942(16)
C(15)-C(16)	1.3815(19)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.383(2)
C(16)-H(16A)	0.9500
C(17)-C(18)	1.3836(19)
C(17)-H(17A)	0.9500
C(18)-C(19)	1.3887(18)
C(18)-H(18A)	0.9500
C(19)-H(19A)	0.9500
C(20)-C(25)	1.3944(17)
C(20)-C(21)	1.3976(17)
C(21)-C(22)	1.3853(18)
C(21)-H(21A)	0.9500
C(22)-C(23)	1.3831(19)
C(22)-H(22A)	0.9500
C(23)-C(24)	1.3839(19)
C(23)-H(23A)	0.9500
C(24)-C(25)	1.3874(17)
C(24)-H(24A)	0.9500
C(25)-H(25A)	0.9500

O(31)-C(43)	1.2256(14)
N(31)-C(43)	1.3729(15)
N(31)-C(34)	1.4281(14)
N(31)-C(31)	1.4875(14)
C(31)-C(32)	1.5331(16)
C(31)-H(31A)	0.9900
C(31)-H(31B)	0.9900
C(32)-C(33)	1.5153(15)
C(32)-H(32A)	0.9900
C(32)-H(32B)	0.9900
C(33)-C(34)	1.3758(16)
C(33)-C(42)	1.4222(16)
C(34)-C(35)	1.4178(16)
C(35)-C(36)	1.4219(16)
C(35)-C(40)	1.4248(16)
C(36)-C(37)	1.3691(17)
C(36)-H(36A)	0.9500
C(37)-C(38)	1.4118(18)
C(37)-H(37A)	0.9500
C(38)-C(39)	1.3670(17)
C(38)-H(38A)	0.9500
C(39)-C(40)	1.4248(16)

C(39)-H(39A)	0.9500
C(40)-C(41)	1.4168(16)
C(41)-C(42)	1.3850(16)
C(41)-H(41A)	0.9500
C(42)-C(50)	1.4908(16)
C(43)-C(44)	1.4987(16)
C(44)-C(49)	1.3897(18)
C(44)-C(45)	1.3925(17)
C(45)-C(46)	1.3836(18)
C(45)-H(45A)	0.9500
C(46)-C(47)	1.386(2)
C(46)-H(46A)	0.9500
C(47)-C(48)	1.384(2)
C(47)-H(47A)	0.9500
C(48)-C(49)	1.3906(18)
C(48)-H(48A)	0.9500
C(49)-H(49A)	0.9500
C(50)-C(51)	1.3987(17)
C(50)-C(55)	1.4010(16)
C(51)-C(52)	1.3887(17)
C(51)-H(51A)	0.9500
C(52)-C(53)	1.3877(18)

C(52)-H(52A)	0.9500
C(53)-C(54)	1.3861(18)
C(53)-H(53A)	0.9500
C(54)-C(55)	1.3894(17)
C(54)-H(54A)	0.9500
C(55)-H(55B)	0.9500

C(13)-N(1)-C(4)	118.48(9)
C(13)-N(1)-C(1)	123.22(10)
C(4)-N(1)-C(1)	105.70(9)
N(1)-C(1)-C(2)	103.48(9)
N(1)-C(1)-H(1A)	111.1
C(2)-C(1)-H(1A)	111.1
N(1)-C(1)-H(1B)	111.1
C(2)-C(1)-H(1B)	111.1
H(1A)-C(1)-H(1B)	109.0
C(3)-C(2)-C(1)	102.20(10)
C(3)-C(2)-H(2A)	111.3
C(1)-C(2)-H(2A)	111.3
C(3)-C(2)-H(2B)	111.3
C(1)-C(2)-H(2B)	111.3
H(2A)-C(2)-H(2B)	109.2

C(4)-C(3)-C(12)	120.76(11)
C(4)-C(3)-C(2)	109.40(10)
C(12)-C(3)-C(2)	129.83(11)
C(3)-C(4)-C(5)	123.16(11)
C(3)-C(4)-N(1)	110.32(10)
C(5)-C(4)-N(1)	126.44(11)
C(4)-C(5)-C(6)	124.89(11)
C(4)-C(5)-C(10)	115.95(11)
C(6)-C(5)-C(10)	119.12(11)
C(7)-C(6)-C(5)	120.58(11)
C(7)-C(6)-H(6A)	119.7
C(5)-C(6)-H(6A)	119.7
C(6)-C(7)-C(8)	120.51(12)
C(6)-C(7)-H(7A)	119.7
C(8)-C(7)-H(7A)	119.7
C(9)-C(8)-C(7)	120.44(11)
C(9)-C(8)-H(8A)	119.8
C(7)-C(8)-H(8A)	119.8
C(8)-C(9)-C(10)	120.65(11)
C(8)-C(9)-H(9A)	119.7
C(10)-C(9)-H(9A)	119.7
C(11)-C(10)-C(9)	121.22(11)

C(11)-C(10)-C(5)	120.07(11)
C(9)-C(10)-C(5)	118.71(11)
C(12)-C(11)-C(10)	122.45(11)
C(12)-C(11)-H(11A)	118.8
C(10)-C(11)-H(11A)	118.8
C(11)-C(12)-C(3)	117.49(11)
C(11)-C(12)-C(20)	121.48(10)
C(3)-C(12)-C(20)	121.03(10)
O(1)-C(13)-N(1)	121.30(11)
O(1)-C(13)-C(14)	120.22(10)
N(1)-C(13)-C(14)	118.46(10)
C(19)-C(14)-C(15)	119.82(11)
C(19)-C(14)-C(13)	123.56(10)
C(15)-C(14)-C(13)	116.56(11)
C(16)-C(15)-C(14)	120.15(12)
C(16)-C(15)-H(15A)	119.9
C(14)-C(15)-H(15A)	119.9
C(15)-C(16)-C(17)	120.05(12)
C(15)-C(16)-H(16A)	120.0
C(17)-C(16)-H(16A)	120.0
C(16)-C(17)-C(18)	119.97(12)
C(16)-C(17)-H(17A)	120.0

C(18)-C(17)-H(17A)	120.0
C(17)-C(18)-C(19)	120.51(12)
C(17)-C(18)-H(18A)	119.7
C(19)-C(18)-H(18A)	119.7
C(18)-C(19)-C(14)	119.46(11)
C(18)-C(19)-H(19A)	120.3
C(14)-C(19)-H(19A)	120.3
C(25)-C(20)-C(21)	118.10(11)
C(25)-C(20)-C(12)	120.75(11)
C(21)-C(20)-C(12)	121.15(11)
C(22)-C(21)-C(20)	120.69(12)
C(22)-C(21)-H(21A)	119.7
C(20)-C(21)-H(21A)	119.7
C(23)-C(22)-C(21)	120.45(12)
C(23)-C(22)-H(22A)	119.8
C(21)-C(22)-H(22A)	119.8
C(22)-C(23)-C(24)	119.65(12)
C(22)-C(23)-H(23A)	120.2
C(24)-C(23)-H(23A)	120.2
C(23)-C(24)-C(25)	120.00(12)
C(23)-C(24)-H(24A)	120.0
C(25)-C(24)-H(24A)	120.0

C(24)-C(25)-C(20)	121.10(12)
C(24)-C(25)-H(25A)	119.5
C(20)-C(25)-H(25A)	119.5
C(43)-N(31)-C(34)	122.82(10)
C(43)-N(31)-C(31)	123.91(9)
C(34)-N(31)-C(31)	106.79(9)
N(31)-C(31)-C(32)	103.15(9)
N(31)-C(31)-H(31A)	111.1
C(32)-C(31)-H(31A)	111.1
N(31)-C(31)-H(31B)	111.1
C(32)-C(31)-H(31B)	111.1
H(31A)-C(31)-H(31B)	109.1
C(33)-C(32)-C(31)	102.45(9)
C(33)-C(32)-H(32A)	111.3
C(31)-C(32)-H(32A)	111.3
C(33)-C(32)-H(32B)	111.3
C(31)-C(32)-H(32B)	111.3
H(32A)-C(32)-H(32B)	109.2
C(34)-C(33)-C(42)	120.65(10)
C(34)-C(33)-C(32)	108.78(10)
C(42)-C(33)-C(32)	130.56(10)
C(33)-C(34)-C(35)	123.18(10)

C(33)-C(34)-N(31)	110.52(10)
C(35)-C(34)-N(31)	126.06(10)
C(34)-C(35)-C(36)	124.94(11)
C(34)-C(35)-C(40)	116.10(10)
C(36)-C(35)-C(40)	118.78(10)
C(37)-C(36)-C(35)	120.50(12)
C(37)-C(36)-H(36A)	119.8
C(35)-C(36)-H(36A)	119.8
C(36)-C(37)-C(38)	120.76(11)
C(36)-C(37)-H(37A)	119.6
C(38)-C(37)-H(37A)	119.6
C(39)-C(38)-C(37)	120.14(11)
C(39)-C(38)-H(38A)	119.9
C(37)-C(38)-H(38A)	119.9
C(38)-C(39)-C(40)	120.76(11)
C(38)-C(39)-H(39A)	119.6
C(40)-C(39)-H(39A)	119.6
C(41)-C(40)-C(35)	119.93(10)
C(41)-C(40)-C(39)	121.20(11)
C(35)-C(40)-C(39)	118.81(11)
C(42)-C(41)-C(40)	122.74(11)
C(42)-C(41)-H(41A)	118.6

C(40)-C(41)-H(41A)	118.6
C(41)-C(42)-C(33)	117.20(10)
C(41)-C(42)-C(50)	119.79(10)
C(33)-C(42)-C(50)	123.00(10)
O(31)-C(43)-N(31)	122.38(11)
O(31)-C(43)-C(44)	119.94(10)
N(31)-C(43)-C(44)	117.54(10)
C(49)-C(44)-C(45)	119.50(11)
C(49)-C(44)-C(43)	122.00(11)
C(45)-C(44)-C(43)	117.84(11)
C(46)-C(45)-C(44)	120.36(13)
C(46)-C(45)-H(45A)	119.8
C(44)-C(45)-H(45A)	119.8
C(45)-C(46)-C(47)	120.10(12)
C(45)-C(46)-H(46A)	119.9
C(47)-C(46)-H(46A)	119.9
C(48)-C(47)-C(46)	119.74(12)
C(48)-C(47)-H(47A)	120.1
C(46)-C(47)-H(47A)	120.1
C(47)-C(48)-C(49)	120.43(13)
C(47)-C(48)-H(48A)	119.8
C(49)-C(48)-H(48A)	119.8

C(44)-C(49)-C(48)	119.83(12)
C(44)-C(49)-H(49A)	120.1
C(48)-C(49)-H(49A)	120.1
C(51)-C(50)-C(55)	118.03(11)
C(51)-C(50)-C(42)	122.00(10)
C(55)-C(50)-C(42)	119.92(10)
C(52)-C(51)-C(50)	120.90(11)
C(52)-C(51)-H(51A)	119.6
C(50)-C(51)-H(51A)	119.6
C(53)-C(52)-C(51)	120.35(12)
C(53)-C(52)-H(52A)	119.8
C(51)-C(52)-H(52A)	119.8
C(54)-C(53)-C(52)	119.52(11)
C(54)-C(53)-H(53A)	120.2
C(52)-C(53)-H(53A)	120.2
C(53)-C(54)-C(55)	120.28(11)
C(53)-C(54)-H(54A)	119.9
C(55)-C(54)-H(54A)	119.9
C(54)-C(55)-C(50)	120.92(11)
C(54)-C(55)-H(55B)	119.5
C(50)-C(55)-H(55B)	119.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C25H19NO. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	28(1)	20(1)	30(1)	-2(1)	2(1)	3(1)
N(1)	21(1)	23(1)	23(1)	-3(1)	-3(1)	3(1)
C(1)	21(1)	29(1)	26(1)	-6(1)	-3(1)	6(1)
C(2)	21(1)	37(1)	25(1)	-3(1)	-2(1)	4(1)
C(3)	21(1)	20(1)	26(1)	-2(1)	-1(1)	1(1)
C(4)	22(1)	17(1)	25(1)	-2(1)	-4(1)	3(1)
C(5)	22(1)	15(1)	26(1)	0(1)	-1(1)	2(1)
C(6)	25(1)	20(1)	27(1)	2(1)	-2(1)	1(1)
C(7)	27(1)	23(1)	29(1)	4(1)	4(1)	0(1)
C(8)	21(1)	23(1)	37(1)	2(1)	2(1)	0(1)
C(9)	22(1)	19(1)	32(1)	1(1)	-4(1)	1(1)
C(10)	22(1)	15(1)	28(1)	-1(1)	-2(1)	1(1)
C(11)	22(1)	18(1)	25(1)	0(1)	-6(1)	1(1)
C(12)	22(1)	18(1)	25(1)	-1(1)	-3(1)	1(1)
C(13)	25(1)	16(1)	23(1)	3(1)	2(1)	-2(1)

C(14)	24(1)	21(1)	19(1)	0(1)	2(1)	-4(1)
C(15)	31(1)	22(1)	28(1)	-4(1)	4(1)	-4(1)
C(16)	35(1)	32(1)	27(1)	-10(1)	3(1)	-13(1)
C(17)	29(1)	44(1)	19(1)	1(1)	-3(1)	-12(1)
C(18)	33(1)	29(1)	31(1)	8(1)	-8(1)	-5(1)
C(19)	31(1)	20(1)	28(1)	1(1)	-7(1)	-6(1)
C(20)	20(1)	19(1)	26(1)	2(1)	-2(1)	4(1)
C(21)	24(1)	23(1)	31(1)	0(1)	-2(1)	0(1)
C(22)	22(1)	23(1)	40(1)	6(1)	3(1)	2(1)
C(23)	29(1)	30(1)	29(1)	7(1)	5(1)	8(1)
C(24)	30(1)	30(1)	25(1)	-1(1)	-3(1)	5(1)
C(25)	22(1)	23(1)	28(1)	2(1)	-2(1)	1(1)
O(31)	25(1)	24(1)	24(1)	-2(1)	-4(1)	1(1)
N(31)	25(1)	18(1)	19(1)	-1(1)	-1(1)	-3(1)
C(31)	30(1)	20(1)	21(1)	-2(1)	-2(1)	-6(1)
C(32)	27(1)	18(1)	19(1)	0(1)	-1(1)	-2(1)
C(33)	18(1)	18(1)	22(1)	-1(1)	-2(1)	1(1)
C(34)	16(1)	19(1)	22(1)	0(1)	-2(1)	1(1)
C(35)	16(1)	20(1)	22(1)	-2(1)	-3(1)	2(1)
C(36)	20(1)	24(1)	25(1)	-2(1)	-3(1)	1(1)
C(37)	24(1)	27(1)	26(1)	-9(1)	-4(1)	3(1)
C(38)	22(1)	20(1)	37(1)	-8(1)	-6(1)	0(1)

C(39)	19(1)	20(1)	32(1)	-1(1)	-4(1)	-1(1)
C(40)	15(1)	20(1)	26(1)	-2(1)	-3(1)	1(1)
C(41)	17(1)	19(1)	24(1)	1(1)	-1(1)	0(1)
C(42)	17(1)	19(1)	22(1)	0(1)	-1(1)	1(1)
C(43)	24(1)	19(1)	20(1)	-3(1)	1(1)	4(1)
C(44)	32(1)	20(1)	17(1)	-4(1)	2(1)	1(1)
C(45)	37(1)	21(1)	22(1)	-4(1)	2(1)	6(1)
C(46)	53(1)	21(1)	22(1)	0(1)	0(1)	6(1)
C(47)	57(1)	26(1)	21(1)	0(1)	8(1)	-7(1)
C(48)	39(1)	36(1)	26(1)	-3(1)	6(1)	-9(1)
C(49)	33(1)	29(1)	21(1)	0(1)	-1(1)	-3(1)
C(50)	17(1)	20(1)	22(1)	0(1)	0(1)	-4(1)
C(51)	26(1)	22(1)	23(1)	2(1)	0(1)	0(1)
C(52)	32(1)	24(1)	26(1)	-3(1)	3(1)	0(1)
C(53)	32(1)	33(1)	20(1)	-1(1)	3(1)	-5(1)
C(54)	30(1)	29(1)	23(1)	7(1)	-2(1)	-6(1)
C(55)	24(1)	19(1)	25(1)	2(1)	-1(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C25H19NO.

	x	y	z	U(eq)
H(1A)	1680	3891	518	30
H(1B)	2032	5207	664	30
H(2A)	1987	4190	1330	33
H(2B)	1932	2695	1123	33
H(6A)	3556	3865	-41	29
H(7A)	4515	3936	-125	32
H(8A)	5110	3661	477	32
H(9A)	4741	3308	1160	29
H(11A)	3923	3084	1643	26
H(15A)	1987	836	-339	32
H(16A)	1207	801	-793	38
H(17A)	760	2819	-978	37
H(18A)	1080	4867	-697	37
H(19A)	1837	4908	-217	32
H(21A)	2248	1716	1754	31
H(22A)	1879	1448	2446	34
H(23A)	2278	2573	3035	35
H(24A)	3067	3932	2930	34
H(25A)	3434	4223	2237	29

H(31A)	6302	6164	2404	28
H(31B)	6753	5059	2566	28
H(32A)	6257	5221	3199	26
H(32B)	5690	5659	2952	26
H(36A)	6057	1837	1729	27
H(37A)	5888	-415	1576	31
H(38A)	5477	-1843	2098	31
H(39A)	5295	-1044	2787	28
H(41A)	5394	757	3338	24
H(45A)	5439	6256	1286	32
H(46A)	5859	7759	803	39
H(47A)	6834	7925	770	42
H(48A)	7385	6632	1237	40
H(49A)	6966	5207	1748	33
H(51A)	5322	5015	3612	28
H(52A)	5199	5578	4339	33
H(53A)	5388	3991	4882	34
H(54A)	5728	1851	4693	33
H(55B)	5863	1287	3967	27

Table 6. Torsion angles [°] for C25H19NO.

C(13)-N(1)-C(1)-C(2)	111.53(11)
C(4)-N(1)-C(1)-C(2)	-29.39(12)
N(1)-C(1)-C(2)-C(3)	27.05(12)
C(1)-C(2)-C(3)-C(4)	-15.87(13)
C(1)-C(2)-C(3)-C(12)	162.64(12)
C(12)-C(3)-C(4)-C(5)	-4.13(18)
C(2)-C(3)-C(4)-C(5)	174.54(10)
C(12)-C(3)-C(4)-N(1)	178.95(10)
C(2)-C(3)-C(4)-N(1)	-2.38(13)
C(13)-N(1)-C(4)-C(3)	-122.65(11)
C(1)-N(1)-C(4)-C(3)	20.48(12)
C(13)-N(1)-C(4)-C(5)	60.55(15)
C(1)-N(1)-C(4)-C(5)	-156.32(11)
C(3)-C(4)-C(5)-C(6)	-175.65(11)
N(1)-C(4)-C(5)-C(6)	0.76(18)
C(3)-C(4)-C(5)-C(10)	2.07(16)
N(1)-C(4)-C(5)-C(10)	178.48(10)
C(4)-C(5)-C(6)-C(7)	177.68(11)
C(10)-C(5)-C(6)-C(7)	0.03(17)
C(5)-C(6)-C(7)-C(8)	0.17(18)
C(6)-C(7)-C(8)-C(9)	0.04(18)

C(7)-C(8)-C(9)-C(10)	-0.46(18)
C(8)-C(9)-C(10)-C(11)	-178.25(11)
C(8)-C(9)-C(10)-C(5)	0.64(17)
C(4)-C(5)-C(10)-C(11)	0.62(15)
C(6)-C(5)-C(10)-C(11)	178.48(10)
C(4)-C(5)-C(10)-C(9)	-178.28(10)
C(6)-C(5)-C(10)-C(9)	-0.43(16)
C(9)-C(10)-C(11)-C(12)	177.57(11)
C(5)-C(10)-C(11)-C(12)	-1.31(17)
C(10)-C(11)-C(12)-C(3)	-0.62(17)
C(10)-C(11)-C(12)-C(20)	179.45(10)
C(4)-C(3)-C(12)-C(11)	3.28(17)
C(2)-C(3)-C(12)-C(11)	-175.09(12)
C(4)-C(3)-C(12)-C(20)	-176.79(11)
C(2)-C(3)-C(12)-C(20)	4.84(19)
C(4)-N(1)-C(13)-O(1)	-9.30(16)
C(1)-N(1)-C(13)-O(1)	-145.63(11)
C(4)-N(1)-C(13)-C(14)	172.00(10)
C(1)-N(1)-C(13)-C(14)	35.66(15)
O(1)-C(13)-C(14)-C(19)	-144.80(12)
N(1)-C(13)-C(14)-C(19)	33.92(17)
O(1)-C(13)-C(14)-C(15)	32.38(16)

N(1)-C(13)-C(14)-C(15)	-148.90(11)
C(19)-C(14)-C(15)-C(16)	-2.02(18)
C(13)-C(14)-C(15)-C(16)	-179.31(11)
C(14)-C(15)-C(16)-C(17)	2.08(19)
C(15)-C(16)-C(17)-C(18)	-0.61(19)
C(16)-C(17)-C(18)-C(19)	-0.9(2)
C(17)-C(18)-C(19)-C(14)	1.0(2)
C(15)-C(14)-C(19)-C(18)	0.49(18)
C(13)-C(14)-C(19)-C(18)	177.59(11)
C(11)-C(12)-C(20)-C(25)	42.66(16)
C(3)-C(12)-C(20)-C(25)	-137.26(12)
C(11)-C(12)-C(20)-C(21)	-136.67(12)
C(3)-C(12)-C(20)-C(21)	43.40(16)
C(25)-C(20)-C(21)-C(22)	1.48(17)
C(12)-C(20)-C(21)-C(22)	-179.17(11)
C(20)-C(21)-C(22)-C(23)	-0.46(18)
C(21)-C(22)-C(23)-C(24)	-0.92(19)
C(22)-C(23)-C(24)-C(25)	1.24(19)
C(23)-C(24)-C(25)-C(20)	-0.19(18)
C(21)-C(20)-C(25)-C(24)	-1.16(17)
C(12)-C(20)-C(25)-C(24)	179.49(11)
C(43)-N(31)-C(31)-C(32)	124.87(11)

C(34)-N(31)-C(31)-C(32)	-27.40(11)
N(31)-C(31)-C(32)-C(33)	27.29(11)
C(31)-C(32)-C(33)-C(34)	-18.61(12)
C(31)-C(32)-C(33)-C(42)	160.65(11)
C(42)-C(33)-C(34)-C(35)	-2.94(17)
C(32)-C(33)-C(34)-C(35)	176.41(10)
C(42)-C(33)-C(34)-N(31)	-177.54(10)
C(32)-C(33)-C(34)-N(31)	1.81(13)
C(43)-N(31)-C(34)-C(33)	-136.00(11)
C(31)-N(31)-C(34)-C(33)	16.64(12)
C(43)-N(31)-C(34)-C(35)	49.59(16)
C(31)-N(31)-C(34)-C(35)	-157.77(11)
C(33)-C(34)-C(35)-C(36)	-169.82(11)
N(31)-C(34)-C(35)-C(36)	3.91(18)
C(33)-C(34)-C(35)-C(40)	5.24(16)
N(31)-C(34)-C(35)-C(40)	178.97(10)
C(34)-C(35)-C(36)-C(37)	178.30(11)
C(40)-C(35)-C(36)-C(37)	3.36(17)
C(35)-C(36)-C(37)-C(38)	0.99(18)
C(36)-C(37)-C(38)-C(39)	-2.75(18)
C(37)-C(38)-C(39)-C(40)	0.04(17)
C(34)-C(35)-C(40)-C(41)	-4.01(15)

C(36)-C(35)-C(40)-C(41)	171.37(10)
C(34)-C(35)-C(40)-C(39)	178.71(10)
C(36)-C(35)-C(40)-C(39)	-5.91(16)
C(38)-C(39)-C(40)-C(41)	-172.97(11)
C(38)-C(39)-C(40)-C(35)	4.28(16)
C(35)-C(40)-C(41)-C(42)	0.63(17)
C(39)-C(40)-C(41)-C(42)	177.85(10)
C(40)-C(41)-C(42)-C(33)	1.83(16)
C(40)-C(41)-C(42)-C(50)	-179.26(10)
C(34)-C(33)-C(42)-C(41)	-0.73(16)
C(32)-C(33)-C(42)-C(41)	-179.91(11)
C(34)-C(33)-C(42)-C(50)	-179.60(10)
C(32)-C(33)-C(42)-C(50)	1.21(18)
C(34)-N(31)-C(43)-O(31)	-0.05(17)
C(31)-N(31)-C(43)-O(31)	-148.04(11)
C(34)-N(31)-C(43)-C(44)	-175.83(10)
C(31)-N(31)-C(43)-C(44)	36.19(15)
O(31)-C(43)-C(44)-C(49)	-136.80(12)
N(31)-C(43)-C(44)-C(49)	39.08(16)
O(31)-C(43)-C(44)-C(45)	33.82(16)
N(31)-C(43)-C(44)-C(45)	-150.29(10)
C(49)-C(44)-C(45)-C(46)	-0.75(17)

C(43)-C(44)-C(45)-C(46)	-171.62(11)
C(44)-C(45)-C(46)-C(47)	1.78(18)
C(45)-C(46)-C(47)-C(48)	-1.01(19)
C(46)-C(47)-C(48)-C(49)	-0.8(2)
C(45)-C(44)-C(49)-C(48)	-1.02(18)
C(43)-C(44)-C(49)-C(48)	169.45(11)
C(47)-C(48)-C(49)-C(44)	1.79(19)
C(41)-C(42)-C(50)-C(51)	-141.33(11)
C(33)-C(42)-C(50)-C(51)	37.52(16)
C(41)-C(42)-C(50)-C(55)	35.94(15)
C(33)-C(42)-C(50)-C(55)	-145.21(11)
C(55)-C(50)-C(51)-C(52)	-0.37(17)
C(42)-C(50)-C(51)-C(52)	176.95(11)
C(50)-C(51)-C(52)-C(53)	-0.48(19)
C(51)-C(52)-C(53)-C(54)	0.93(19)
C(52)-C(53)-C(54)-C(55)	-0.54(19)
C(53)-C(54)-C(55)-C(50)	-0.31(18)
C(51)-C(50)-C(55)-C(54)	0.76(17)
C(42)-C(50)-C(55)-C(54)	-176.62(11)

Symmetry transformations used to generate equivalent atoms:

The thermal ellipsoid of tetrahydro indenopyridine **4.23a** drawn at 50% probability level. The CCDC number is 895233

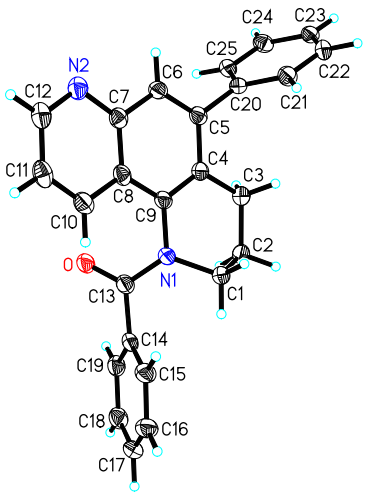


Table 1. Crystal data and structure refinement for $C_{25}H_{20}N_2O$.

Identification code	q03c
Empirical formula	$C_{25}H_{20}N_2O$
Formula weight	364.43
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic

Space group	P2(1)	
Unit cell dimensions	a = 8.1060(2) Å	α= 90°.
	b = 5.9470(2) Å	β= 101.3800(10)°.
	c = 19.3890(5) Å	γ = 90°.
Volume	916.30(4) $Å^3$	
Z	2	
Density (calculated)	1.321 Mg/m^3	
Absorption coefficient	0.635 mm^{-1}	
F(000)	384	
Crystal size	0.19 x 0.05 x 0.04 mm^3	
Theta range for data collection	2.32 to 68.69°.	
Index ranges	-9<=h<=8, -7<=k<=6, -23<=l<=23	
Reflections collected	7765	
Independent reflections	2767 [R(int) = 0.0196]	
Completeness to theta = 66.00°	98.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.886	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2767 / 1 / 253	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R1 = 0.0272, wR2 = 0.0725	

R indices (all data)	R1 = 0.0275, wR2 = 0.0728
Absolute structure parameter	0.0(2)
Largest diff. peak and hole	0.159 and -0.121 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for C25H20N2O. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O	3209(1)	3108(2)	1143(1)	29(1)
N(1)	2383(1)	3758(2)	2187(1)	27(1)
N(2)	7798(2)	7717(2)	2519(1)	29(1)
C(1)	1256(2)	2928(3)	2643(1)	32(1)
C(2)	1897(2)	672(3)	2943(1)	32(1)
C(3)	3688(2)	882(3)	3376(1)	28(1)
C(4)	4703(2)	2761(3)	3133(1)	23(1)
C(5)	6374(2)	3158(3)	3520(1)	23(1)
C(6)	7366(2)	4736(3)	3289(1)	24(1)
C(7)	6748(2)	6109(3)	2699(1)	24(1)
C(8)	5057(2)	5843(3)	2339(1)	25(1)
C(9)	4086(2)	4068(3)	2554(1)	24(1)
C(10)	4438(2)	7415(3)	1800(1)	29(1)

C(11)	5484(2)	9039(3)	1638(1)	32(1)
C(12)	7162(2)	9094(3)	2005(1)	31(1)
C(13)	2075(2)	3256(3)	1474(1)	25(1)
C(14)	275(2)	3001(3)	1109(1)	25(1)
C(15)	-937(2)	4595(3)	1180(1)	29(1)
C(16)	-2567(2)	4379(3)	803(1)	33(1)
C(17)	-3002(2)	2558(3)	360(1)	34(1)
C(18)	-1806(2)	969(3)	284(1)	33(1)
C(19)	-160(2)	1199(3)	652(1)	29(1)
C(20)	7036(2)	1828(3)	4170(1)	23(1)
C(21)	6616(2)	2413(3)	4815(1)	28(1)
C(22)	7204(2)	1125(3)	5413(1)	29(1)
C(23)	8210(2)	-730(3)	5376(1)	26(1)
C(24)	8653(2)	-1291(3)	4744(1)	28(1)
C(25)	8069(2)	-16(3)	4146(1)	25(1)

Table 3. Bond lengths [Å] and angles [°] for C25H20N2O.

O-C(13)	1.2235(16)
N(1)-C(13)	1.3865(17)
N(1)-C(9)	1.4351(17)

N(1)-C(1)	1.4764(18)
N(2)-C(12)	1.315(2)
N(2)-C(7)	1.3708(19)
C(1)-C(2)	1.513(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.532(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.518(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(9)	1.376(2)
C(4)-C(5)	1.4332(19)
C(5)-C(6)	1.368(2)
C(5)-C(20)	1.495(2)
C(6)-C(7)	1.414(2)
C(6)-H(6)	0.9500
C(7)-C(8)	1.4191(19)
C(8)-C(10)	1.417(2)
C(8)-C(9)	1.427(2)
C(10)-C(11)	1.362(2)

C(10)-H(10)	0.9500
C(11)-C(12)	1.405(2)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.4992(19)
C(14)-C(19)	1.391(2)
C(14)-C(15)	1.391(2)
C(15)-C(16)	1.384(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.384(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.382(2)
C(17)-H(17)	0.9500
C(18)-C(19)	1.390(2)
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(20)-C(25)	1.386(2)
C(20)-C(21)	1.4035(19)
C(21)-C(22)	1.392(2)
C(21)-H(21)	0.9500
C(22)-C(23)	1.382(2)
C(22)-H(22)	0.9500

C(23)-C(24)	1.384(2)
C(23)-H(23)	0.9500
C(24)-C(25)	1.387(2)
C(24)-H(24)	0.9500
C(25)-H(25)	0.9500

C(13)-N(1)-C(9)	119.19(10)
C(13)-N(1)-C(1)	120.92(12)
C(9)-N(1)-C(1)	113.25(11)
C(12)-N(2)-C(7)	117.18(13)
N(1)-C(1)-C(2)	108.68(12)
N(1)-C(1)-H(1A)	110.0
C(2)-C(1)-H(1A)	110.0
N(1)-C(1)-H(1B)	110.0
C(2)-C(1)-H(1B)	110.0
H(1A)-C(1)-H(1B)	108.3
C(1)-C(2)-C(3)	110.82(13)
C(1)-C(2)-H(2A)	109.5
C(3)-C(2)-H(2A)	109.5
C(1)-C(2)-H(2B)	109.5
C(3)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	108.1

C(4)-C(3)-C(2)	113.71(12)
C(4)-C(3)-H(3A)	108.8
C(2)-C(3)-H(3A)	108.8
C(4)-C(3)-H(3B)	108.8
C(2)-C(3)-H(3B)	108.8
H(3A)-C(3)-H(3B)	107.7
C(9)-C(4)-C(5)	119.25(13)
C(9)-C(4)-C(3)	122.56(12)
C(5)-C(4)-C(3)	118.18(12)
C(6)-C(5)-C(4)	119.78(12)
C(6)-C(5)-C(20)	120.23(12)
C(4)-C(5)-C(20)	119.99(12)
C(5)-C(6)-C(7)	121.59(12)
C(5)-C(6)-H(6)	119.2
C(7)-C(6)-H(6)	119.2
N(2)-C(7)-C(6)	117.99(12)
N(2)-C(7)-C(8)	122.74(13)
C(6)-C(7)-C(8)	119.20(13)
C(10)-C(8)-C(7)	117.14(14)
C(10)-C(8)-C(9)	124.61(13)
C(7)-C(8)-C(9)	118.23(13)
C(4)-C(9)-C(8)	121.59(12)

C(4)-C(9)-N(1)	119.41(12)
C(8)-C(9)-N(1)	118.83(12)
C(11)-C(10)-C(8)	119.50(13)
C(11)-C(10)-H(10)	120.3
C(8)-C(10)-H(10)	120.3
C(10)-C(11)-C(12)	118.89(14)
C(10)-C(11)-H(11)	120.6
C(12)-C(11)-H(11)	120.6
N(2)-C(12)-C(11)	124.45(14)
N(2)-C(12)-H(12)	117.8
C(11)-C(12)-H(12)	117.8
O-C(13)-N(1)	122.16(12)
O-C(13)-C(14)	120.42(12)
N(1)-C(13)-C(14)	117.36(11)
C(19)-C(14)-C(15)	119.54(13)
C(19)-C(14)-C(13)	118.66(13)
C(15)-C(14)-C(13)	121.66(13)
C(16)-C(15)-C(14)	120.25(15)
C(16)-C(15)-H(15)	119.9
C(14)-C(15)-H(15)	119.9
C(15)-C(16)-C(17)	120.02(14)
C(15)-C(16)-H(16)	120.0

C(17)-C(16)-H(16)	120.0
C(18)-C(17)-C(16)	120.15(14)
C(18)-C(17)-H(17)	119.9
C(16)-C(17)-H(17)	119.9
C(17)-C(18)-C(19)	120.05(15)
C(17)-C(18)-H(18)	120.0
C(19)-C(18)-H(18)	120.0
C(18)-C(19)-C(14)	119.97(14)
C(18)-C(19)-H(19)	120.0
C(14)-C(19)-H(19)	120.0
C(25)-C(20)-C(21)	118.70(13)
C(25)-C(20)-C(5)	120.63(12)
C(21)-C(20)-C(5)	120.67(13)
C(22)-C(21)-C(20)	120.11(14)
C(22)-C(21)-H(21)	119.9
C(20)-C(21)-H(21)	119.9
C(23)-C(22)-C(21)	120.32(12)
C(23)-C(22)-H(22)	119.8
C(21)-C(22)-H(22)	119.8
C(22)-C(23)-C(24)	119.80(13)
C(22)-C(23)-H(23)	120.1
C(24)-C(23)-H(23)	120.1

C(23)-C(24)-C(25)	120.13(13)
C(23)-C(24)-H(24)	119.9
C(25)-C(24)-H(24)	119.9
C(20)-C(25)-C(24)	120.91(13)
C(20)-C(25)-H(25)	119.5
C(24)-C(25)-H(25)	119.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C25H20N2O. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O	26(1)	41(1)	20(1)	2(1)	6(1)	8(1)
N(1)	20(1)	43(1)	18(1)	0(1)	3(1)	3(1)
N(2)	34(1)	28(1)	25(1)	-1(1)	9(1)	-2(1)
C(1)	22(1)	55(1)	20(1)	-2(1)	5(1)	-1(1)
C(2)	27(1)	45(1)	24(1)	-3(1)	8(1)	-9(1)
C(3)	26(1)	34(1)	23(1)	0(1)	6(1)	-1(1)
C(4)	22(1)	28(1)	20(1)	-3(1)	6(1)	1(1)
C(5)	23(1)	26(1)	19(1)	-3(1)	5(1)	4(1)

C(6)	22(1)	28(1)	21(1)	-3(1)	3(1)	1(1)
C(7)	27(1)	25(1)	21(1)	-2(1)	7(1)	3(1)
C(8)	28(1)	29(1)	19(1)	-1(1)	7(1)	5(1)
C(9)	21(1)	34(1)	18(1)	-3(1)	4(1)	4(1)
C(10)	29(1)	35(1)	22(1)	1(1)	6(1)	10(1)
C(11)	45(1)	28(1)	25(1)	5(1)	11(1)	11(1)
C(12)	43(1)	28(1)	26(1)	0(1)	12(1)	-1(1)
C(13)	26(1)	30(1)	20(1)	1(1)	4(1)	5(1)
C(14)	26(1)	33(1)	16(1)	2(1)	4(1)	2(1)
C(15)	27(1)	36(1)	23(1)	-4(1)	3(1)	2(1)
C(16)	26(1)	42(1)	29(1)	0(1)	3(1)	8(1)
C(17)	26(1)	50(1)	22(1)	4(1)	0(1)	-3(1)
C(18)	37(1)	41(1)	21(1)	-5(1)	5(1)	-7(1)
C(19)	32(1)	33(1)	22(1)	-1(1)	9(1)	2(1)
C(20)	19(1)	29(1)	21(1)	0(1)	2(1)	-4(1)
C(21)	26(1)	33(1)	24(1)	-1(1)	5(1)	6(1)
C(22)	28(1)	40(1)	20(1)	-1(1)	8(1)	0(1)
C(23)	25(1)	30(1)	22(1)	4(1)	1(1)	-5(1)
C(24)	28(1)	27(1)	27(1)	-2(1)	1(1)	4(1)
C(25)	26(1)	30(1)	20(1)	-3(1)	4(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C25H20N2O.

	x	y	z	U(eq)
H(1A)	96	2769	2367	39
H(1B)	1234	4009	3029	39
H(2A)	1890	-410	2554	38
H(2B)	1142	86	3245	38
H(3A)	3625	1146	3875	33
H(3B)	4285	-560	3352	33
H(6)	8498	4914	3530	28
H(10)	3303	7337	1555	34
H(11)	5086	10116	1282	38
H(12)	7885	10200	1872	38
H(15)	-645	5835	1489	35
H(16)	-3387	5482	848	39
H(17)	-4126	2400	107	40
H(18)	-2109	-281	-19	39
H(19)	668	125	592	34
H(21)	5928	3690	4844	33

H(22)	6913	1523	5848	35
H(23)	8596	-1618	5783	32
H(24)	9358	-2552	4719	33
H(25)	8381	-412	3715	30

Table 6. Torsion angles [°] for C25H20N2O.

C(13)-N(1)-C(1)-C(2)	90.57(15)
C(9)-N(1)-C(1)-C(2)	-60.60(16)
N(1)-C(1)-C(2)-C(3)	59.93(15)
C(1)-C(2)-C(3)-C(4)	-28.89(17)
C(2)-C(3)-C(4)-C(9)	-3.10(19)
C(2)-C(3)-C(4)-C(5)	177.58(12)
C(9)-C(4)-C(5)-C(6)	-3.73(19)
C(3)-C(4)-C(5)-C(6)	175.61(13)
C(9)-C(4)-C(5)-C(20)	177.15(13)
C(3)-C(4)-C(5)-C(20)	-3.51(19)
C(4)-C(5)-C(6)-C(7)	4.4(2)
C(20)-C(5)-C(6)-C(7)	-176.46(12)
C(12)-N(2)-C(7)-C(6)	-174.75(13)
C(12)-N(2)-C(7)-C(8)	2.2(2)

C(5)-C(6)-C(7)-N(2)	177.13(13)
C(5)-C(6)-C(7)-C(8)	0.0(2)
N(2)-C(7)-C(8)-C(10)	-3.7(2)
C(6)-C(7)-C(8)-C(10)	173.26(12)
N(2)-C(7)-C(8)-C(9)	178.02(12)
C(6)-C(7)-C(8)-C(9)	-5.02(19)
C(5)-C(4)-C(9)-C(8)	-1.40(19)
C(3)-C(4)-C(9)-C(8)	179.28(12)
C(5)-C(4)-C(9)-N(1)	-176.62(12)
C(3)-C(4)-C(9)-N(1)	4.1(2)
C(10)-C(8)-C(9)-C(4)	-172.40(13)
C(7)-C(8)-C(9)-C(4)	5.74(19)
C(10)-C(8)-C(9)-N(1)	2.8(2)
C(7)-C(8)-C(9)-N(1)	-179.02(12)
C(13)-N(1)-C(9)-C(4)	-123.22(15)
C(1)-N(1)-C(9)-C(4)	28.49(19)
C(13)-N(1)-C(9)-C(8)	61.43(19)
C(1)-N(1)-C(9)-C(8)	-146.85(13)
C(7)-C(8)-C(10)-C(11)	2.08(19)
C(9)-C(8)-C(10)-C(11)	-179.77(13)
C(8)-C(10)-C(11)-C(12)	0.7(2)
C(7)-N(2)-C(12)-C(11)	0.9(2)

C(10)-C(11)-C(12)-N(2)	-2.4(2)
C(9)-N(1)-C(13)-O	-1.4(2)
C(1)-N(1)-C(13)-O	-150.88(15)
C(9)-N(1)-C(13)-C(14)	-178.55(13)
C(1)-N(1)-C(13)-C(14)	31.9(2)
O-C(13)-C(14)-C(19)	47.6(2)
N(1)-C(13)-C(14)-C(19)	-135.16(15)
O-C(13)-C(14)-C(15)	-128.14(16)
N(1)-C(13)-C(14)-C(15)	49.1(2)
C(19)-C(14)-C(15)-C(16)	0.5(2)
C(13)-C(14)-C(15)-C(16)	176.17(13)
C(14)-C(15)-C(16)-C(17)	0.8(2)
C(15)-C(16)-C(17)-C(18)	-1.0(2)
C(16)-C(17)-C(18)-C(19)	-0.2(2)
C(17)-C(18)-C(19)-C(14)	1.5(2)
C(15)-C(14)-C(19)-C(18)	-1.6(2)
C(13)-C(14)-C(19)-C(18)	-177.44(13)
C(6)-C(5)-C(20)-C(25)	-80.47(18)
C(4)-C(5)-C(20)-C(25)	98.64(15)
C(6)-C(5)-C(20)-C(21)	99.91(16)
C(4)-C(5)-C(20)-C(21)	-80.98(18)
C(25)-C(20)-C(21)-C(22)	-1.3(2)

C(5)-C(20)-C(21)-C(22)	178.32(13)
C(20)-C(21)-C(22)-C(23)	0.3(2)
C(21)-C(22)-C(23)-C(24)	0.9(2)
C(22)-C(23)-C(24)-C(25)	-1.0(2)
C(21)-C(20)-C(25)-C(24)	1.2(2)
C(5)-C(20)-C(25)-C(24)	-178.38(13)
C(23)-C(24)-C(25)-C(20)	-0.1(2)

Symmetry transformations used to generate equivalent atoms: